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A Multi-method Investigation of the Acquisition and Treatment of Pathological Fear

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A Multi-Method Investigation of the Acquisition and Treatment of Pathological Fear

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A Multi-Method Investigation of the Acquisition and Treatment of Pathological Fear

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Abstract: Over the course of their lifetime, about 25% of the U.S. population will meet criteria for one or more of the anxiety-related disorders, all of which are characterized by pathological fear responding. Researchers have made significant strides in improving treatment efficacy through the development of cognitive-behavioral models for understanding the acquisition and treatment of pathological fear. Although cognitive-behavioral treatments produce marked reductions in pathological fear on average, a subgroup of patients do not respond to treatment. In an effort to improve the prevention and treatment of pathological fear, this dissertation synthesizes data from a series of studies aimed to (a) improve our understanding of factors that contribute to the development of pathological fear in a real-world setting (Study 1), (b) examine factors that influence response to exposure therapy, a technique used across gold-standard treatments pathological fear (Study 2), and (c) investigate novel strategies that could be added to exposure therapy to further improve treatment response (Study 3). Specifically, Study 1 demonstrates the contribution of cognitive appraisal (i.e., threat perception) to the onset of pathological fear in response to stressors encountered in a real-world, high-stress environment (warzone deployment). Study 2 is a meta-analysis exploring the influence of unnecessary protective actions, or safety behaviors (SBs), on outcomes of

exposure therapy. Data demonstrate that removing SBs during exposure therapy improves treatment outcomes, whereas adding SBs during exposure therapy produces inferior outcomes under certain conditions, such as when treating specific phobia symptoms. Finally, Study 3 is a randomized clinical trial investigating the use of two behavioral strategies, alone and in combination, to enhance exposure therapy outcomes: (1) a brief pre-exposure fear memory reactivation trial (PE-FMR) and (2) deepened extinction. Results suggest that neither PE-FMR nor deepened extinction improve outcomes at post-treatment or one-week follow-up. However, PE-FMR augmentation produced more rapid fear reduction during treatment, and equivalent outcomes even when the duration of exposure therapy (tailored to speed of fear reduction) was shorted by 21% on average. Together, these lines of research contribute to our understanding of cognitive and behavioral influences on the development and treatment of pathological fear.

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GENERAL INTRODUCTION

At some point in their lifetime, about one in four people in the U.S. will meet criteria for an anxiety-related disorder (Kessler et al., 2005). These disorders are associated with a host of consequences, including reduced quality of life (Mendlowicz & Stein, 2000), and work impairment (Greenberg et al., 1999), as well as increased risk for physical disorders and disability (Sareen, Cox, Clara, & Asmundson, 2005), substance use disorders (Grant et al., 2004), depression (Wittchen, Kessler, Pfister, Höfler, & Lieb, 2000), and suicidal ideation and attempts (Sareen et al., 2005). The economic burden of anxiety disorders is also substantial, with direct and indirect costs estimated at more than 42 billion dollars per year in the U.S. alone (Greenberg et al., 1999).

Due to the heavy cost and consequences of anxiety disorders, decades of research have focused on developing models for understanding their onset and maintenance, with the aim of boosting treatment efficacy. Though anxiety disorders span a wide variety of clinical presentations, they share the common element of a persistent and pathological fear response. For this reason, the models and treatments for anxiety disorders have more similarities than differences. In support of this idea, researchers have succeeded in developing several trans-diagnostic treatments for anxiety disorders that target their common maintaining factors (Barlow et al., 2010; Schmidt et al., 2012). Similarly, recent recommendations put forth by the National Institutes of Health suggest that researchers focus on common domains across diagnostic categories, such as the domains of potential and active threat (anxiety/fear), rather than studying particular diagnostic categories (Morris & Cuthbert, 2012). In line with these recommendations, the synthesis of research in this dissertation will focus on a trans-diagnostic view of pathological fear.

The projects in this dissertation will build upon prior research in the development of cognitive behavioral and neurobiological models for understanding the onset and treatment of pathological fear. Specifically, study 1 is an investigation of the role of cognitive appraisal (i.e., perceived threat) in the onset of pathological fear in response to environmental stressors. Study 2 will use meta-analytic methods to investigate the impact of safety behaviors (i.e., unnecessary protective actions), on the reduction of pathological fear during psychotherapy. Finally, study 3 is an investigation of two behavioral strategies for enhancing exposure-based treatments of pathological fear: (1) fear memory reactivation, developed from the neurobiological model of fear reduction via reconsolidation update mechanisms; and (2) deepened extinction, based on the model of fear reduction via prediction error. Together, these lines of research contribute to the further development of cognitive behavioral models for the acquisition and treatment of pathological fear. Before describing these studies in more detail, this chapter will set the backdrop by briefly summarizing relevant models for the onset and treatment of pathological fear, discussing the current status of psychotherapy for pathological fear, and reviewing prior research on treatment augmentation.

Models of Fear Acquisition and Extinction

BEHAVIORAL MODELS

Fear Conditioning and Extinction

Pavlov (1927) developed one of the earliest behavioral models of fear acquisition with his description of classical conditioning. Applying the model of classical conditioning to fear specifically, the model suggests that fear can be acquired by the repeated pairing of a neutral stimulus with an aversive stimulus, until the neutral stimulus develops a conditioned association with the aversive stimulus, such that it begins to independently produce an aversive response. Watson and Rayner (1920) demonstrated this process of fear acquisition in their "little Albert" experiment. Young Albert first expressed interest in a white rat, but after repeated pairings of the white rat (neutral stimulus) with a loud and unpleasant noise (unconditioned stimulus), Albert eventually displayed fear (conditioned response) when presented with the white rat (conditioned stimulus). This classical conditioning model represents one of the earliest explanations of fear acquisition. Operant conditioning (Skinner, 1938) helped to explain its maintenance.

Operant conditioning suggests that behavioral responses that are paired with reinforcement or reward will increase over time, whereas responses that are not reinforced or are punished will decrease over time. Mowrer's two factor learning theory (1960) applied operant conditioning to the maintenance of fear responding. Specifically, the theory describes how avoidance or escape from a feared stimulus is negatively reinforced by a reduction in fear. Furthermore, avoidance and escape from the feared stimulus then perpetuates its association with threat because escape and avoidance prevent the possibility of new experiences that could extinguish the fear response.

From these behavioral models of fear acquisition and maintenance, it logically follows that repeated exposure to the feared stimulus in the absence of the feared

consequence extinguishes the fear response. In other words, after repeated presentations of the conditioned stimulus (CS) in the absence of the unconditioned stimulus (UCS), the CS eventually ceases to produce the conditioned response (CR). This behavioral procedure is referred to as fear extinction in the animal literature, and as exposure therapy in the psychotherapy literature.

Counter-conditioning and Reciprocal Inhibition

Mary Cover Jones (1924) was among the first to document the use of exposure therapy to treat pathological fear. Before therapy, her participant, young Peter, had a strong fear response to a white rabbit. After repeated, non-threatening encounters with the rabbit, Peter's fear of the rabbit eventually extinguished, and he displayed marked progress in his ability to approach the rabbit. This describes a classic extinction procedure used to reduce fear responding. During the second stage of treatment, Jones elaborated on the procedure by pairing the presentation of the rabbit with food Peter likes (candy), with the idea that this would condition a new, positive association with the rabbit. This process, pairing the stimulus with a new unconditioned stimulus to produce a new conditioned response, is called counter-conditioning.

Wolpe (1954; 1968) took the theory of counter-conditioning a step further with his idea of reciprocal inhibition. Reciprocal inhibition was inspired by the law of reciprocal innervation, demonstrating that smooth limb movement occurs because flexing one muscle produces automatic relaxation of the opposing muscle (Ciuffreda & Stark, 1975). Wolpe (1968) analogously suggested treating pathological fear by pairing the presentation of the feared stimulus with relaxation, a physiological state inhibitory to the fear response. He developed a treatment procedure based on this technique called systematic desensitization. Patients first mastered self-induced relaxation through several sessions of training in progressive muscle relaxation. They then were instructed to

imagine confronting the feared stimulus (a process called imaginal exposure), very gradually increasing the difficulty of the imagined situations while maintaining a physiological state of relaxation. Whenever their anxiety increased, patients were instructed to pause imaginal exposure to regain a physiological state of relaxation. Although systematic desensitization was among the first empirically supported treatments for anxiety, it fell out of favor as soon as researchers demonstrated that patients have equal or superior responses to exposure therapy in the absence of relaxation training and graduated stimulus presentation procedures (Boulougouris, Marks & Marset, 1971; Emmelkamp, 1974; Keane, Fairbank, Caddell, & Zimering, 1989).

Problems with Behavioral Models

Although basic conditioning models of fear acquisition and extinction dominated the field for several decades, researchers began to uncover several phenomena that could not be accounted for by conditioning models. For example, studies demonstrated that many cases of phobia are not preceded by a traumatic/conditioning event (Öst, 1991; Poulton, Davies, Menzies, Langley, & Silva, 1998), and that certain phobias are more easily conditioned and extinguished in the laboratory than others (Mineka & Ohman, 2002). Furthermore, evidence suggests that the acquisition and extinction of fear can be facilitated through social learning. For example, acquisition can be facilitated by watching another individual have a fearful response to the stimulus (Rachman, 1977), and extinction can be facilitated by watching another individual model successfully coping with the feared stimulus (Askew & Field, 2007; Dunne & Askew, 2013). Additionally the basic conditioning theories cannot explain why many individuals experience traumatic events without developing conditioned fear responses (Rachman, 1977). Cognitive-behavioral models of fear acquisition and extinction were developed to account for the shortcomings of strictly behavioral, conditioning models.

COGNITIVE-BEHAVIORAL MODELS

Cognitive-behavioral models extend beyond behavioral models. These theories primarily emphasize that it is not just exposure to particular situations, but the perception and cognitive processing of those situations, that determines behavioral and emotional responses (Bandura, Adams, & Beyer, 1977; Clark & Beck, 2011; Clark & Wells, 1995; Ehlers & Clark, 2000). A number of theories describing the acquisition and treatment of pathological fear fall under the umbrella of cognitive-behavioral models.

Emotional processing theory (EPT) is a well-known cognitive-behavioral theory of fear reduction. EPT is based on the foundation of Lang's bioinformational theory and Rachman's (1980) proposal of the construct of emotional processing, but Foa and Kozak's (1986) elaboration of the theory is perhaps the version that is the most frequently cited. Foa and Kozak (1986) defined emotional processing as "the modification of memory structures that underlie emotions" (p. 20). They broke fear memory structures into three components: (1) characteristics of the feared stimulus; (2) responses to the feared stimulus (verbal, physiological, and behavioral responses); and (3) interpretive meaning of the stimulus and responses. They described two key elements of treatments that modify pathological fear structures: (1) initial activation of the fear structure during treatment, and (2) confrontation with, and incorporation of, information incompatible with the fear structure. Finally, they proposed three signs that emotional processing is occurring (1) initial fear activation, (2) within-session habituation, and (3) between-session habituation.

A more recent update to emotional processing theory incorporated newer findings, such as data demonstrating a lack of correlation between within-session habituation and treatment outcomes (Foa, Huppert, & Cahill, 2006). Authors suggest that the most critical component of the theory is confrontation with threat-disconfirming

information, and conclude that within-session habituation, therefore, should only provide threat disconfirmation for individuals who have a belief that their anxiety will continue indefinitely unless they escape from the feared situation. The critical role of attention to, and interpretation of, threat in emotional processing theory highlights its key cognitive component.

Expectancy theory also falls under this cognitive-behavioral umbrella (Reiss, Peterson, Gursky, & McNally, 1986). This theory suggests that fear response can be predicted by probability of harm (danger) added to the product of the probability of experiencing anxiety with anxiety sensitivity (i.e., dispositional tendency to respond fearfully to fear itself). Note that this model highlights the critical role of the cognitive predisposing factor of anxiety sensitivity in predicting fear response. On the basis of this model, Reiss and McNally suggest that fear should decrease when (1) the expectancy of harm decreases, and (2) when the expectancy of anxiety decreases for individuals with anxiety sensitivity. Later models elaborated further on this theory, adding elements such as social evaluation expectancy and rejection sensitivity (Reiss, 1991); for individuals with social evaluation sensitivity, fear should decrease when their expectancy of social evaluation decreases. Similar to EPT, this model also emphasizes the important role of the cognitive appraisal of experiences, such as anxiety and social evaluation, in governing the onset and attenuation of fear.

Bandura's famous self-efficacy theory would also fall under the umbrella of cognitive-behavioral models, in that he describes the role of perceiving an inability to cope with a given situation in governing fear acquisition, and the role of increased perception of mastery or ability to cope with a particular situation in facilitating fear reduction (Bandura, 1988). Bandura posits that changes in self-efficacy can occur by acquiring new information from four different sources: (1) performance

accomplishments, including direct experiences such as those that occur in exposure therapy, (2) vicarious experiences, such as witnessing another person interact with the feared stimulus, (3) verbal persuasion, such as being persuaded that one has the skills necessary to cope with the feared situation, and (4) emotional arousal, such as interpreting lower physiological arousal in the presence of the feared stimulus as an indicator of increased coping ability (Bandura, 1977). The concept of self-efficacy extends beyond beliefs about the ability to cope with a situation behaviorally, and includes beliefs about the ability to cope with thoughts and feelings while in a fear-provoking situation (Valentiner, Telch, Petruzi, & Bolte, 1996). The central role of perceived coping ability is the putative mediator of fear onset and attenuation in this model.

NEUROBIOLOGICAL MODELS

Although he did not propose a neurobiological model, Pavlov (1927) was one of the first to propose that, rather than unlearning a fear during extinction training, a new memory is created that inhibits the fear response. Evidence for the persistence of the original fear memory after extinction has emerged over time, as researchers gathered data demonstrating that fear can return after extinction under a variety of conditions, such as after the passage of time (spontaneous recovery of fear), after a change in context (fear renewal), and after re-exposure to the unconditioned stimulus (reinstatement; Bouton, 2002).

The original fear memory is labile, and susceptible to disruption or updating during a 6-hour window of time while its biological structure is solidifying, or consolidating (Schafe & LeDoux, 2000). Similarly, researchers have found that when a fear memory is primed by a brief confrontation with the feared stimulus, the memory structure re-enters a 6-hour labile window and requires additional protein synthesis to

persist. During this time, the original fear memory trace is susceptible to disruption or updating (Monfils, Cowansage, Klann, & LeDoux, 2009; Nader, Schafe, & Le Doux, 2000). If new information about the feared stimulus is encountered during this period of memory lability, the information overwrites or updates the original fear memory. This process is called the "reconsolidation update" mechanism. It will be reviewed in further detail in study 3, which will use a brief fear memory reactivation trial before exposure therapy in an effort to trigger reconsolidation update rather than inhibitory learning. Overall, it is important to note that new inhibitory learning and reconsolidation update are the primary putative mechanisms in contemporary neurobiological models of fear attenuation during extinction training.

Psychotherapy for Pathological Fear and Anxiety: Current Status

Despite extensive research on models of the onset, maintenance, and treatment of anxiety, many people with anxiety disorders do not receive treatment. For example, in a study of primary care patients in the U.S., more than 40% of people with anxiety disorders reported no current treatment (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007). Due to sampling from a healthcare setting in a first-world country, this study likely overestimates treatment seeking in comparison with the world population. In line with this idea, an international study found that more than 55% of people worldwide with panic disorder, generalized, anxiety disorder, or OCD, do not receive treatment (Kohn, Saxena, Levav, & Saraceno, 2004). Other findings have been even more pessimistic, suggesting that less than 30% of individuals with anxiety disorders seek treatment (Leon, Portera, & Weissman, 1995). Though the exact statistic differs across studies, these data provide a clear picture of the substantial gap between the need for, and use of, mental health services among individuals with anxiety disorders.

Across the variety of psychotherapeutic approaches for anxiety treatment, cognitive-behavioral therapy has emerged as the modality with the strongest empirical support, with meta-analyses demonstrating medium to large effect sizes across anxiety disorders (Butler, Chapman, Forman, & Beck, 2006; Hofmann & Smits, 2008; Norton & Price, 2007). However, a substantial number of patients do not respond to treatment. An examination of a sample of randomized controlled trials (RCTs) suggests that approximately 15 to 35% of patients who receive gold-standard treatments for anxiety disorders do not respond to treatment (see Table 1 for example studies).

Table 1: Response and remission rates after gold-standard psychotherapy in a sample of randomized controlled trials across anxiety disorders.

Citation	Disorder	Treatment	% Responders
Telch et al., 1993	Panic Disorder	Group Panic Inoculation Training	37% did not meet criteria for recovery at 6-month follow-up
Ladouceur et al., 2000	Generalized Anxiety Disorder	Cognitive Behavioral Treatment	23% still met diagnostic criteria for GAD at 6 and 12-month follow up
Foa, Liebowitz et al., 2005	Obsessive-Compulsive Disorder	Exposure and Response Prevention	14% of treatment completers were classified as non-responders
Clark et al., 2006	Social Anxiety Disorder	Cognitive Therapy	16% still met diagnostic criteria at post-treatment
Foa et al., 1999	Posttraumatic Stress Disorder	Prolonged Exposure	35% of treatment completers still met diagnostic criteria at 1-year follow-up

This statistic is likely even an overestimation of the response rate to CBT in the community, since RCTs provide therapists with access to training and supervision resources well beyond those typically available in community settings. This problem has spurred decades of research in an effort to improve the available interventions for anxiety disorders.

Improving Intervention: Exposure Therapy Augmentation Research

Across the various cognitive-behavioral treatment packages for anxiety disorders, exposure therapy is among the most potent and commonly used treatment techniques. Many researchers, therefore, have sought to identify methods to enhance exposure therapy, using both pharmacological and non-pharmacological techniques.

PHARMACOLOGICAL AUGMENTATIONS

Pharmacological augmentation of exposure therapy can be thought of as falling into two categories: anxiolytic pharmacotherapy, and cognitive-enhancing pharmacotherapy. The use of anxiolytic pharmacotherapy as an augmentation strategy for exposure-based treatments has a long history of disappointing outcomes (see Telch, Tearnan, & Taylor, 1983). A systematic review of the literature revealed little to no benefit of adding medication to gold-standard treatments for anxiety (Otto, McHugh, & Kantak, 2010). In fact, some findings suggest that combining CBT with anxiolytic medications can even lead to more relapse in the long-run than CBT alone (Otto et al., 2010).

In contrast, experimenters have produced promising findings for a number of cognitive enhancers, such as D-Cycloserine (DCS; Norberg, Krystal, & Tolin, 2008), yohimbine (Holmes & Quirk, 2010; Powers, Smits, Otto, Sanders, & Emmelkamp, 2009), glucocorticoids (Soravia et al., 2006) and Methylene Blue (Telch, Bruchey, Rosenfield, Cobb, & Smits, 2014). However, evidence suggests that the benefits of DCS attenuate across sessions, leading researchers to propose that its main benefit is in improving the speed of fear reduction during treatment (Norberg et al., 2008). Furthermore, many patients are reluctant to use medications. For instance, a recent survey of anxiety patients identified a strong preference for cognitive-behavioral over

pharmacological treatment methods (Deacon & Abramowitz, 2005). Non-pharmacological strategies also would be more readily available to a wider array of mental health settings and could even be translated into self-directed treatment, thus providing a more cost-efficient solution to treatment augmentation.

NON-PHARMACOLOGICAL AUGMENTATIONS

Many researchers have explored non-pharmacological strategies to boost the efficacy of exposure therapy. Some of these strategies simply manipulate the parameters by which exposure therapy is implemented, such as massing versus spacing exposure therapy sessions (Foa, Jameson, Turner, & Payne, 1980), presenting feared stimuli in a graduated or non-graduated manner (Everaerd, Rijken, & Emmelkamp, 1973), using imaginal or in vivo presentation of feared stimuli (Emmelkamp & Wessels, 1975), conducting treatment in individual or group settings (O'Connor et al., 2005), or providing exposure therapy with or without the therapist present (Gloster et al., 2011). There appears to be relatively strong evidence for the advantage of therapist-directed over self-directed exposure, and in vivo exposure over imaginal exposure; although findings are generally more mixed for the manipulation of other parameters (see Telch, Cobb, & Lancaster, 2014 for a review).

Another line of research has focused on the augmentation of exposure therapy through the addition of cognitive or behavioral strategies. For example, relaxation training in the form of "breathing retraining" has been added to multi-component cognitive-behavioral treatment manuals for anxiety (Barlow & Craske, 2006; Foa, Hembree, & Rothbaum, 2007). An earlier incarnation of exposure therapy called systematic desensitization also combined relaxation (in the form of progressive muscle relaxation) with exposure therapy (Wolpe, 1958). In both instances, researchers have demonstrated that adding relaxation training to exposure therapy does not improve

outcomes (Boulougouris, Marks, & Marset, 1971; de Ruiter, Ryken, Garssen, & Kraaimaat, 1989; Deacon et al., 2012; Schmidt et al., 2000).

Other exposure augmentation strategies have been more successful. For instance, several studies have demonstrated that exposure therapy is more effective when therapists incorporate modeling effective strategies for coping with anxiety (Bandura, Blanchard, & Ritter, 1969; Blanchard, 1970; Denney, Sullivan, & Thiry, 1977). Although in need of replication, there are also promising preliminary findings for augmentation strategies such as providing physiological feedback during treatment as evidence of fear reduction (Telch, Valentiner, Ilai, Petruzzi, & Hehmsoth, 2000), and using antagonistic actions during exposure therapy (i.e., actions opposite to anxiety-related action tendencies; Wolitzky & Telch, 2009). Findings have been more mixed for other augmentation strategies. For example, some research suggests that the addition of cognitive therapy strategies enhances the efficacy of exposure therapy (Bryant et al., 2008; Kamphuis & Telch, 2000; Taylor, 1996), whereas other studies suggest that exposure therapy works equally well with or without cognitive therapy techniques (Feske & Chambless, 1995; Foa, Hembree, et al., 2005).

Similarly, the findings in regard to safety behavior use during exposure therapy have also been mixed. Safety behaviors can be defined as, "unnecessary actions taken to prevent, escape from, or reduce the severity of a perceived threat" (Telch & Lancaster, 2012, p. 315). Some randomized controlled trials have demonstrated that allowing the patients to use safety behaviors during exposure therapy detracts from its efficacy (Powers, Smits, & Telch, 2004; Sloan & Telch, 2002). However, other studies have found no differences between groups, leading some researchers to the conclusion that safety behavior use does not impact treatment efficacy (Deacon, Sy, Lickel, & Nelson, 2010). Others even suggest that safety behavior use might be beneficial in some ways,

such as making exposure therapy more acceptable to patients (Milosevic & Radomsky, 2013). However, a qualitative review of exposure therapy studies with and without fading of safety behaviors suggests that this form of safety behavior manipulation produces more consistent treatment benefits (Telch & Lancaster, 2012). Although the search for exposure therapy augmentation strategies has been ongoing for the last several decades, relatively few strategies (such as incorporating therapist assistance and modeling during exposure) have emerged as consistently beneficial.

Overview of Dissertation Studies

This dissertation includes three studies that collectively aim to expand upon prior research related to cognitive behavioral models for the acquisition and treatment of pathological fear. Each study uses a different methodology to address this over-arching goal. Study 1 uses observational methods to investigate the role of threat perception in the onset of anxiety and related disorders, in an effort to provide clarification about the mechanisms of the development of pathological anxiety, and to identify early markers of psychopathology to assist in targeting at-risk populations. Study 2 employs meta-analysis to examine the impact of safety behavior use and fading on the treatment of pathological fear in the context of exposure therapy. Finally, study 3 is a randomized controlled trial investigating two behavioral strategies for enhancing the efficacy and efficiency of exposure therapy: fear memory reactivation, predicated on the neurobiological mechanism of reconsolidation update; and deepened extinction, predicated the mechanism of prediction error.

STUDY 1: IS WARZONE THREAT PERCEPTION ASSOCIATED WITH ONSET OF STRESS-RELATED PATHOLOGY FOR SOLDIERS DURING DEPLOYMENT?

Cognitive-behavioral models of stress (Lazarus & Folkman, 1984), emotional disorders (Beck, 1979; Clark & Beck, 2011), and general psychological functioning (Bandura, 1986; 1988) suggest that cognitive appraisal plays a central role in the human stress response. In line with this idea, prior studies have found that threat perception correlates with the onset of PTSD (Ozer, Best, Lipsey, & Weiss, 2003). However, a significant weakness of prior research in this area is the use of retrospective measures of threat perception, particularly because the onset of posttraumatic symptoms increases the retrospective recall of threat perceived during the traumatic event (Southwick & Morgan, 1997). This study reports on the use a novel, web-based strategy to collect data in the

deployed setting to assess the association of threat perception with the early onset of PTSD symptoms (and concurrent symptoms of depression) in the deployed setting. The identification of early risk factors such as threat perception plays a key role in targeting at-risk groups for preventive interventions in active duty military personnel, a population with a significant gap between the need for, and use of, mental health services (Hoge et al., 2004; Tanielian & Jaycox, 2009). Furthermore, this research provides an additional step toward establishing the causal role of threat appraisal in the onset of PTSD.

STUDY 2: DOES SAFETY BEHAVIOR USE IMPACT THE EFFICACY OF EXPOSURE THERAPY?

Study 2 will build upon prior research investigating the impact of safety behavior use on the efficacy of exposure therapy. Researchers have produced mixed findings with regard to the impact of safety behaviors on exposure therapy, and the issue of whether safety behaviors detract from exposure therapy has become a controversial one in the field (e.g., Rachman, Radomsky, & Shafran, 2008; Parrish, Radomsky, & Dugas, 2008). However, a careful qualitative examination of the evidence to date highlights a number of differences in the way experimenters manipulate safety behaviors, which may in turn impact study findings. For instance, a qualitative review suggests that the impact of fading naturally occurring safety behaviors during exposure therapy consistently produces superior treatment outcomes; however, the influence of investigator-initiated safety behavior use during exposure therapy appears to be much less consistent, with some studies showing no influence and others showing an impendence in fear reduction (Telch & Lancaster, 2012). It is also possible that procedural variations may govern the influence of safety behavior use on treatment outcome, specifically, whether safety behaviors are faded as treatment progresses, or whether they are maintained throughout treatment. Cognitive theories (Salkovskis, 1991) would suggest that maintained safety behaviors would be more detrimental to fear attenuation because the experience of safety

would be misattributed to the safety behavior across all trials, effectively blocking any experience of threat disconfirmation.

Although there have been a number of excellent qualitative reviews of safety behavior use during exposure therapy (Helbig-Lang et al., 2014; Rachman, Radomsky, & Shafran, 2008), there has been only one quantitative, meta-analytic review to date (Meulders, Daela, Volders, & Vlaeyen, 2016). The findings were unfortunately "inconclusive... and could not provide strong evidence supporting either the removal or addition of [safety behaviors] during exposure-based treatment" (p. 151). Notably, there was a moderate to high degree of variance in the effect sizes across studies, suggesting that the strength of effect sizes may depend on certain variables, such as the type of assessment used, the sample of patients, and the procedures by which safety behaviors were manipulated (e.g., selection of investigator initiated versus naturally occurring safety behaviors). Therefore, in addition to examining the overall influence of adding and removing safety behaviors on exposure therapy, study 2 will also use meta-analysis to examine potential moderators of effect size, to explore the conditions under which safety behaviors influence treatment outcomes.

STUDY 3: DO FEAR MEMORY REACTIVATION AND DEEPENED EXTINCTION ENHANCE EXPOSURE THERAPY?

Study 3 will test novel treatment augmentation strategies informed by basic science on the mechanisms of fear extinction. Specifically, recent behavioral neuroscience studies on fear conditioning and extinction studies have revealed two behavioral techniques that seem to enhance fear attenuation: pre-exposure fear memory reactivation (PE-FMR; Monfils et al., 2009) and deepened extinction (Rescorla, 2006). Data suggest that PE-FMR enhances fear reduction by promoting the reconsolidation update mechanism (Monfils et al., 2009), whereas deepened extinction enhances fear

reduction through the error correction mechanism (Leung & Westbrook, 2008). Study 3 will test the independent and combined effects of FPE-MR and deepened extinction on the efficacy of one-session exposure therapy for fear of snakes and spiders.

STUDY 1 - THE ROLE OF PERCEIVED THREAT IN THE EMERGENCE OF PTSD AND DEPRESSION SYMPTOMS DURING WARZONE DEPLOYMENT[1]

Combat-exposed military personnel are four to five times more likely to develop posttraumatic stress disorder (PTSD) relative to those deployed but not exposed (Smith et al., 2008), yet less than 10% develop PTSD symptoms, and fewer meet diagnostic criteria for PTSD (LeardMann et al., 2009). The heterogeneity of warzone-stress reactions (e.g., Dickstein, Suvak, Litz, & Adler, 2010) underscores the importance of identifying factors beyond combat exposure alone that increase risk for experiencing psychological symptoms as a reaction to deployment stress.

It has been well established that appraisal of threat plays a central role in general psychological functioning (Bandura, 1988), stress reactions (Lazarus & Folkman, 1984), and the onset and maintenance of emotional disorders (e.g., Beck et al., 1979). From a theoretical perspective, the impact of a stressor hinges on the individual's appraisal of the demands of the stress relative to their capacity to cope; this cognitive appraisal dictates the response to the event (Lazarus & Folkman, 1984). The perception of threat occurs when the demands of the situation are perceived as exceeding one's capacity to cope. In the short-run, perceived threat can result in activation of the hypothalamic pituitary adrenocortical (HPA) axis, leading to physiologically adaptive compensations such as increased adrenaline to boost one's strength for fleeing or fighting. However, more persistent perception of threat (i.e., chronic stress) is associated with dysregulation of the HPA axis and the onset of illness and psychopathology (Miller, Chen, & Zhou, 2007).

[1] Study published in peer-reviewed journal. Citation: Lancaster, C. L., Cobb, A. R., Lee, H. J., & Telch, M. J. (2016). The role of perceived threat in the emergence of PTSD and depression symptoms during warzone deployment. *Psychological Trauma: Theory, Research, Practice, and Policy*, *8*(4), 528-534.

For instance, prior studies have associated threat perception with depression (Beck et al, 1979), panic and agoraphobia (Clark, 1986; Telch, Brouillard, Telch, Agras, & Taylor, 1989), and PTSD (Ehlers & Clark, 2000).

Perceived threat of warzone experiences has been defined as "fear for one's safety and well-being in the warzone" (L. A. King, King, Vogt, Knight, & Samper, 2006, pg. 98) and is conceptually distinct from the endorsement of warzone stressors. Whereas the measurement of warzone stress refers to frequency of stressors encountered in the warzone, such as endorsing "receiving hostile incoming fire" or "being wounded or injured in combat," warzone threat perception relates to the individual's evaluation of the probability and severity of danger, which can occur at any time during warzone deployment. For instance, the thought, "I was concerned that my unit would be attacked by the enemy," can occur in the absence of one of the specific warzone stressors included on standardized checklists. Furthermore, one could potentially experience a warzone stressor in the absence of perceived danger, such as going on convoy in Iraq in the absence of concerns about receiving incoming fire or encountering an improvised explosive device. Perceived threat has been reliably linked to PTSD and depression in service members across wars, branches, and nationalities (e.g., James, Van Kampen, Miller, & Engdahl, 2013; D. W. King, King, Gudanowski, & Vreven, 1995; Phillips, LeardMann, Gumbs, & Smith 2010; van Wingen, Geuze, Vermetten, & Fernández, 2011). This association has remained after controlling for combat exposure (James et al., 2013; Vogt, Proctor, King, King, & Vasterling, 2008), and importantly, perceived threat has been shown to mediate deployment stressors' impact on post-deployment PTSD (Franz et al., 2013; D. W. King et al., 1995; Renshaw, 2011).

Two fundamental limitations exist in prior investigations of perceived warzone threat and its association with warzone stressors, and the development of

psychopathology. First, warzone threat perception has been assessed retrospectively, months or even years after returning from the warzone (e.g., D W. King et al., 1995; Renshaw, 2011). However, experiencing deployment-related psychopathology may inflate recall of both the frequency of stressors and of threat perception – a hypothesis supported by longitudinal evidence that PTSD amplifies retrospective reports of both threat (Heir et al., 2009) and combat exposure (Engelhard, van den Hout, & McNally, 2008; Southwick et al., 1997). Secondly, studies have yet to test whether perceived threat potentiates the emergence of PTSD and depression symptoms during deployment in response to varying levels of warzone stress exposure.

Here we present new data from the Texas Combat PTSD Risk Project (Lee, Goudarzi, Baldwin, Rosenfield, Telch, 2011; Telch, Rosenfield, Lee, & Pai, 2012), a proof-of-concept prospective risk study focused on identifying risk and resilience factors associated with the emergence of PTSD and depression. A unique feature of the project was the use of a web-based in-theater assessment system in which soldiers provided repeated assessments of warzone stress variables and symptom ratings of PTSD and depression while deployed in Iraq. This study reports new data on the association between perceived threat in the warzone, and the in-theater emergence of PTSD and depression symptoms. We hypothesized that threat perception would be associated with symptoms of PTSD and depression, beyond the effects of warzone stressors and key pre-deployment covariates, including lifetime history of psychopathology. Based on previous work (e.g., D. W. King et al., 1995), we also predicted that threat perception would potentiate warzone stressors' impact on symptoms of PTSD and depression.

Methods

PARTICIPANTS

To enroll in the study, soldiers had to meet the following criteria: (a) age 18 or older, (b) no prior military deployments, and (c) planned deployment to Iraq within 3 months of consent. Among those briefed about the study, 82% (N = 184) provided consent, 6 did not deploy, 1 withdrew, and 16 did not complete assessments, leaving 161 soldiers with viable data. Assessments were excluded if they did not include measures used in this analysis, leaving 308 observations from 150 soldiers, and 302 observations from 146 soldiers for the PTSD and depression models, respectively. According to the last in-theater survey completed, deployment lasted an average of 14.98 months (SD = 2.25; range = 8.00 – 18.43). The sample was predominantly male (88%), White (73%), and young (M = 25.33 years, SD = 6.08, range: 19 - 49 years). Among the soldiers included in the data set, 54% screened positive for lifetime history of an Axis I disorder.

The PI (M. J. T.) and project director briefed soldiers from nine units selected by Army command that were scheduled to deploy from Ft. Hood to Iraq between August 2007 and August 2009. These nine units included four combat units, four combat service support units, and one combat support unit. Unit leaders agreed to uphold the principle of voluntary participation in the study and were not present during the briefing and consent process to mitigate the potential for perceived coercion. During the briefing, soldiers were informed that study participation was completely voluntary and that consent could be withdrawn at any time without penalty. Participants were informed that their data would be de-identified and were reassured by the PI (M. J. T.) and an appointed Army ombudsman (not connected to the project) that the Army would not have access to their data.

Soldiers consented to the parent project, the Texas Combat PTSD Risk Study, a longitudinal study evaluating risk factors for the onset of PTSD and depression in soldiers deployed to Iraq (see Lee et al., 2011 for additional details). Consented soldiers were transported to The University of Texas at Austin to complete a comprehensive pre-deployment assessment battery, including genetic, cognitive, neuroimaging, hormonal, and psychosocial measures. During deployment, soldiers received monthly email reminders to complete the Combat Experience Log (CEL), a de-identified, web-based assessment of warzone stressors and warzone stress reactions. Since it was unlikely that soldiers would be able to complete web-based assessments each month due to the logistical constraints of the deployed setting, they were instructed to complete assessments as frequently as possible. Out of the total number of study participants (N = 177), over 90% (N =161) completed at least one CEL during deployment. Assuming a deployment cycle of 14 months on average, the full data set for the Combat Experiences Log included 42% of the total possible observations (Lee et al., 2011). After elimination of data points with missing data for one or more of the variables used in the present analysis, the final data set for this study included 12% of the total possible observations with a range of 1 to 6 observations per soldier (M = 2.07 observations per soldier; SD = 1.62 for the depression data set; M = 2.05 observations per soldier; SD = 1.61 for the PTSD data set). Data for the present study were drawn from the pre-deployment assessment and the CEL.

PRE-DEPLOYMENT MEASURES

Soldiers completed a comprehensive pre-deployment assessment from which demographics and clinical diagnostic data from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I-IV; First, Spitzer, Gibbon, & Williams, 1996) were used for the present analysis. Doctoral students with at least one year of experience in

diagnostic interviewing administered the SCID, and diagnoses were confirmed in a follow-up interview with the PI (M. J. T.) with perfect agreement between evaluators.

In-Theater Measures

Stressors were assessed with a checklist adapted from the Deployment Risk and Resilience Inventory (DRRI; D. W. King, King, & Vogt, 2003), including 18 items assessing incidence of common deployment stressors, and 2 items allowing report of stressors not on the checklist. Perceived threat during the prior month was assessed using the 15-item Deployment Concerns section of the DRRI (D. W. King et al., 2003). PTSD symptoms within the last month were reported using the validated 4-item version of the PTSD Checklist (Bliese et al., 2008; Weathers, Litz, Herman, Huska, & Keane, 1993), and depression within the past week was reported using the validated 10-item version of the Center for Epidemiological Studies Depression Scale (Andresen, Malmgren, Carter, & Patrick, 1994).

Statistical Analyses

Data were analyzed with random intercept multilevel models using the nlme package in R (Pinheiro, Bates, DebRoy, & Sarkar, 2014; R Core Team, 2014), with repeated observations nested within soldiers. All candidate predictors were entered into the initial model, and then backwards elimination of non-significant effects ($p > .05$) was used to select the final models. Initial models included: (1) gender (male = 0; female = 1), (2) minority status (White = 0; Non-White = 1), (3) lifetime Axis I disorder based on the SCID-IV (absence = 0; presence = 1), (4) months since the start of deployment (linear and quadratic effects), (5) number of deployment stressors, (6) perceived threat, and (7) the stressors by perceived threat interaction. All variables were Z-transformed (including gender, minority status, and lifetime Axis I disorder) to allow comparison across

standardized effect estimates. To probe interactions, perceived threat was centered 1 SD above and below the mean to determine the conditional effects of stressors, given low or high perceived threat (Aiken & West, 1991). Maximum likelihood estimation was used to compare nested models, whereas restricted maximum likelihood estimation was used to generate reported results (Raudenbush & Bryk, 2002; Maas & Hox, 2005). Descriptive statistics for the data set are presented in Table 2.

Table 2: Descriptive statistics for modeled variables.

Variable	N	%	M	SD
Male	132	88	-	-
Caucasian	110	73	-	-
Lifetime Axis I Disorder[a]	81	54	-	-
Total Deployment Duration (Months)[b]	150	-	14.98	2.25
Monthly Deployment Stressors[b, d]	150	-	2.79	2.90
Perceived Threat[b, e, f]	150	-	27.60	10.94
PCL-4[b, e, f]	150	-	5.26	2.13
CES-D-10[c, e, f]	146	-	7.16	4.86

Note. PCL-4 = PTSD Checklist – 4 Items. CES-D-10 = Center for Epidemiological Studies Depression Scale - 10 Items. [a]Reflects presence of lifetime, including current, DSM-IV-TR Axis I disorders based on pre-deployment SCID-IV interview. [b]Based on 308 observations from 150 soldiers. [c]Based on 302 observations from 146 soldiers. [d]Calculated across soldiers. [e]Calculated across soldiers and deployment months. [f]Questionnaire from the Combat Experience Log.

Results

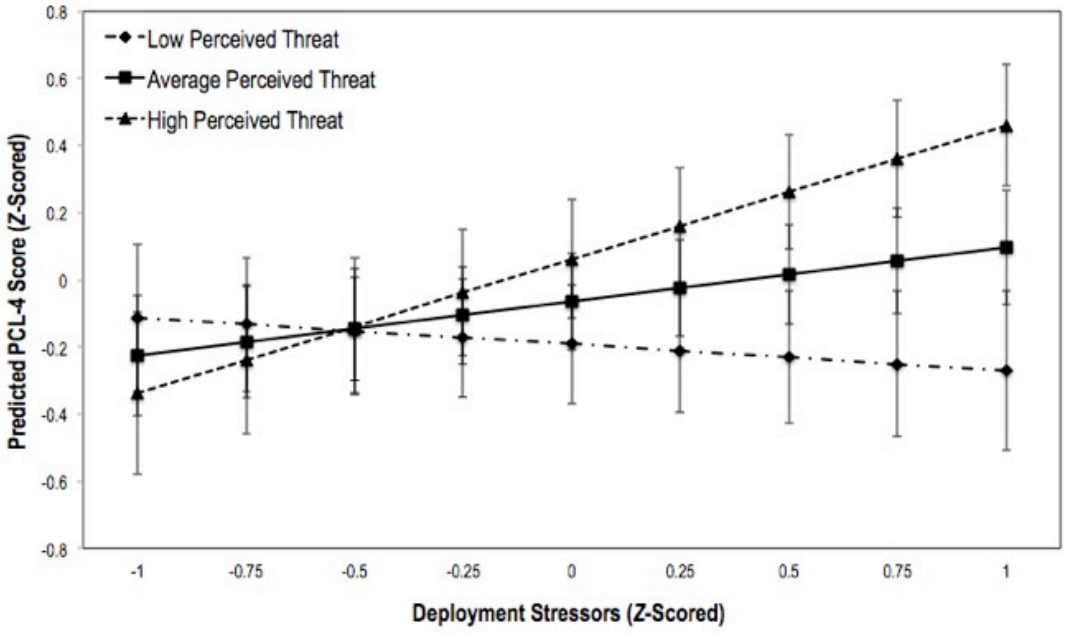
PTSD Model

Starting with the full model for PTSD symptoms, the first step in the backward elimination of non-significant effects was removal of the main effect of minority status from the model (β = -.04, se = .08, p = .584). The second step was removing the quadratic effect of months deployed at the time of survey completion (β = -.05, se = .04, p = .190), the third step was removing the main effect of gender (β = .09, se = .07, p = .196), and the fourth step was removal of the main effect of lifetime history of an Axis I diagnosis (β = .10, se = .07, p = .144). This produced the final model for PTSD symptoms, which included months deployed at the time of survey completion, the main effects of deployment stressors and threat perception, and their interaction (see Table 3).

The finalized model revealed that soldiers reported lower levels of PTSD symptoms at later months in the deployment cycle (β = -0.26, se = .05, p < .001). Assessments included in the present analyses were completed on average closer to the end of the deployment cycle (M = 12.42 months, SD = 3.60 months). This downward trajectory of PTSD symptoms over time is consistent with prior analyses demonstrating that PTSD symptoms decline over the course of the last half of the deployment cycle (Lee et al., 2011). In regard to the primary variables of interest, the final model revealed a significant interaction between deployment stressors and perceived threat, indicating that perceived threat amplified the effect of stressors on PTSD symptoms (β = .24, se = .04, p < .001). Probing revealed a significant impact of stressors on PTSD symptoms for those with high (β = .40, se = .06, p < .001), but not low perceived threat (β = -.08, se = .07, p = .295; see Figure 1). After the removing the interaction term to examine

independent main effects, perceived threat (β = .18, se = .06, p = .002) and stressors (β = .20, se = .05, p < .001) both independently contributed to PTSD symptoms.

Figure 1: Simple effects of low (-1 SD), average, and high (+1 SD) perceived threat on PTSD symptoms (PCL-4) across levels of stressor exposure.



Note. PCL-4 = PTSD Checklist– 4 Items. Error bars reflect 95% confidence intervals.

DEPRESSION MODEL

Starting with the full model for depression symptoms, the first step in the backward elimination procedure was removal of the impact of minority status from the model (β = -.04, se = .07, p = .586). The second step was removal of the stressor by threat interaction (β = .07, se = .05, p = .168). After removing this interaction from the model, the main effect of stressors was non-significant (β = .04, se = .06, p = .537), whereas perceived threat was significantly associated with depression (β = .23, se = .06, p < .001).

After backward elimination of all non-significant predictors, the final model for depression symptoms included gender, lifetime history of an Axis I disorder, the linear

and quadratic effect of deployment month, and perceived threat. In regard to gender, women reported higher levels of depression symptoms during deployment relative to men on average (β = .13, se = .07, p = .051). The final model also revealed that lifetime history of an Axis I disorder conferred risk for depression symptoms during deployment (β = .13, se = .06, p = .044). Furthermore, the combined linear (β = -.23, se = .06, p < .001) and quadratic effect (β = -.14, se = .05, p = .007) of deployment month demonstrated a downward sloping convex relationship, such that the predicted values for depression symptoms increased slightly and then declined across the remaining deployment months. Since assessments included in the present analyses were completed on average closer to the end of the deployment cycle, this downward trajectory of depression symptoms over time is consistent with prior analyses showing the decline in depression symptoms during the latter half of the deployment cycle (Lee et al., 2011). After accounting for gender, history of an Axis I disorder, and the month during deployment at which the survey was completed, increases in perceived threat were found to be associated with increases in depression symptoms during deployment (β = .23, se = .06, p < .001). Final models generated after the removal of all non-significant effects are reported in Table 3.

Table 3: Final Models of PTSD (PCL-4) and depression (CES-D-10) symptoms during deployment.

PTSD Symptoms[a]			
Variable	***β***	**SE *β***	***p***
Intercept	-0.07	0.07	0.369
Months	-0.26	0.05	< .001
Deployment Stressors	0.16	0.05	0.002
Perceived Threat	0.13	0.05	0.020
Stressors x Perceived Threat	0.24	0.04	< .001
Depression Symptoms[b]			
Variable	***β***	**SE *β***	***p***
Intercept	-0.02	0.06	0.780
Gender	0.13	0.07	0.051
Lifetime Axis I Disorder	0.13	0.06	0.044
Months	-0.23	0.06	< .001
Months x Months	-0.14	0.05	0.007
Perceived Threat	0.23	0.06	< .001

Note. PCL-4 = PTSD Checklist – 4 Items. CES-D-10 = Center for Epidemiological Studies Depression Scale - 10 Items. [a]Based on 308 observations from 150 soldiers. [b]Based on 302 observations from 146 soldiers.

Discussion

Summary of Findings

Our overarching aim was to investigate the association between service members' perceived threat of the warzone environment and the emergence of PTSD and depression symptoms. Consistent with our first prediction, perceived threat was associated with the emergence of depression and PTSD symptoms during deployment, independent of warzone stressors. These findings are consistent with prior evidence linking warzone threat perception with PTSD and depression (Franz et al., 2013, James et al., 2013; D. W. King et al., 1995; Renshaw, 2011; Vogt et al., 2008). However, prior studies assessed threat perception months, or even years after deployment (e.g., D. W. King et al., 1995; Renshaw, 2011; Vogt et al., 2008). The in-theater assessments used in this investigation thus strengthen existing evidence by providing support that these effects are not a mere reflection of psychological symptoms inflating retrospective reports of threat perception and stressors in the warzone.

Interestingly, findings also suggest that in-theater reports of warzone stressors and perceived warzone threat impact PTSD and depression symptoms differently. Whereas both warzone stressors and perceived threat independently predicted the emergence of PTSD symptoms, warzone stressors were not associated with depression symptoms after controlling for the effects of perceived threat. Furthermore, our second prediction, that perceived threat would potentiate the effects of warzone stressors, was supported for PTSD symptoms but not for depression. These data provide additional support for prior studies demonstrating the critical role of threat perception in mediating the impact of warzone stressors on PTSD symptoms (Franz et al., 2013; D. W. King et al., 1995; Renshaw, 2011).

IMPLICATIONS

Overall, these data reveal the important association between perceived threat and the onset of PTSD and depression symptoms during warzone deployment. In terms of theoretical implications, findings demonstrate that it is the perception of stressors, and not just their occurrence, that contributes to the development of psychopathology during deployment. Interestingly, findings reveal that threat perception potentiated the onset of PTSD with increased number of warzone stressors, whereas threat perception, but not warzone stressors, predicted depression.

The discrepant effects for perceived threat and warzone stress on depression as compared with PTSD could be related to specific sub-types of stressors associated with these disorders. For example, meta-analytic findings have demonstrated that PTSD is robustly associated with endorsing the perception of threat to one's life (Ozer, Best, Lipsey, & Weiss, 2003), and it is likely that more frequent warzone stressors increase the probability of experiencing one or more life-threatening events. Findings for depression, however, emphasize that the number of warzone stressors has no predictive utility, after controlling for threat perception. Though prior research has demonstrated that life stressors precipitate the onset of depression (Hammen, 2005), all deployed personnel share the general stress associated with military deployment, which includes the interpersonal stressor of displacement from the home environment and support network. Since extensive research has documented the role of interpersonal loss experiences, such as separations, as predictive of the onset of depression (Paykel, 2003), it is possible that the quantity of deployment stressors, over and above the general stress associated with military deployment, is not predictive of depression in the warzone. It may be useful to conduct further research to determine whether specific categories of stressors, such as

interpersonal stressors versus life-threatening stressors, increase the likelihood of depression versus PTSD.

In addition to the theoretical implications, these findings have practical implications. For example, deployed military psychologists could use assessment of perceived threat to identify those service members most at risk for the onset of depression and PTSD symptoms during deployment. This at-risk group could be followed with more frequent screenings and provided with preventive interventions as needed. At-risk service members additionally may benefit from brief psycho-education on the profiles of PTSD and depression symptoms, so that they will have the information needed to recognize when they may benefit from seeking out treatment.

LIMITATIONS

Several study limitations deserve mention. First, although over 90% of our soldier cohort completed one or more in-theater assessments, soldiers often missed monthly assessments (additional information about the missing data and the reasons for it can be found in Lee et al., 2011). The data set used for this study included a maximum of 6 observations per soldier, though soldiers received monthly email reminders to complete assessments, and they were deployed on average for over one year. Future researchers may be able to capture data more consistently during deployment as technology continues to advance, and service members have greater capabilities for accessing web-based surveys throughout the deployment cycle. Furthermore, though data were captured during warzone deployment, the analyses are still cross-sectional, in that threat, stressors, and symptoms were measured simultaneously during deployment, which limits conclusions about the causal influence of warzone stress and threat perception on psychological symptoms. Capturing data more frequently than once per month may allow researchers to produce more powerful prospective models, such as cross-lagged models, to assess

whether warzone stressors and threat perception precede the onset of PTSD and depression symptoms during the subsequent days or weeks. Second, the limited number of observations for several soldiers precluded parsing of the month-to-month changes (time variant effects) from the average (time invariant effects) of perceived threat and deployment stressors. Additionally, this convenience sample of first-time deployed soldiers from nine units stationed at Fort Hood represents a small proportion of the military service personnel deployed to Iraq and may not be representative of military personnel from other Army units or service branches.

Furthermore, due to the necessity for a brief in-theater assessment battery, we used a short, validated assessment of warzone threat perception, rather than assessing the perception of threat associated with each specific warzone stressor. Future researchers may benefit from a more fine-grained assessment, including investigating the variability in threat perception among military personnel in the same unit who experience who experience the same combat stressor. However, even such a fine-grained analysis may have inherent problems regarding differences in each individual's unique experience during the same stressful event; for example, in a unit under enemy fire, some personnel may receive incoming fire at closer proximity than others in their unit.

Finally, the mean levels of PTSD and depression symptoms in our sample indicate that the average soldier assessed during deployment was asymptomatic. While one might argue that the use of such a sample would limit our ability to draw conclusions regarding the development of psychopathology, it is important to bear in mind that post-deployment data suggest that the military personnel who develop PTSD or depression in reaction to warzone stress are in the minority (Smith et al., 2008; Wells et al., 2010). Furthermore, the rates of PTSD and depression observed in our sample during deployment are similar or higher than those observed in prior research at post-

deployment (e.g., Smith et al., 2008; Tanielian & Jaycox, 2008; Wells et al., 2010). Applying cutoff criteria from prior psychometric research to our sample, we averaged soldiers' scores across surveys completed during deployment, and found that 13% exhibited clinically significant levels of PTSD symptoms (total ≥ 7; Bliese et al., 2008), and 23% exhibited clinically significant levels of depression symptoms (total ≥ 10; Andresen et al., 1994). Not only does this document that we have sufficient levels of psychopathology in our sample to test our hypotheses, it also provides evidence that a significant minority of service members experience symptoms of PTSD and depression while still in the deployed setting. The early emergence of PTSD and depression symptoms highlights the need for the identification of acute markers of risk (such as high threat perception) and the development of preventive intervention strategies.

CONCLUSIONS

Our findings are novel in suggesting that in-theater assessment of threat perception is associated with the emergence of PTSD and depression, and that perceived threat amplifies the effects of warzone stressors on PTSD symptoms. The in-theater assessment of these warzone variables provides increased confidence that prior findings are not merely a reflection of psychological symptoms inflating service members' retrospective reporting of warzone stressors and threat perception. Future studies are warranted to determine whether in-theater assessment of warzone and soldier variables more effectively capture the reciprocal interplay between warzone stressors, threat perception, and the emergent trajectories of adaptive and maladaptive stress-reactions.

STUDY 2 - THE EFFECTS OF ADDING OR REMOVING SAFETY BEHAVIORS DURING EXPOSURE THERAPY: A META-ANALYSIS

In the face of threat, humans are hard-wired to engage in protective actions, or safety behaviors. Salkovskis (1991) defined a safety behavior as "overt or covert avoidance of feared outcomes that is carried out within a specific situation." This broad definition encompasses both adaptive and maladaptive safety behaviors. Examples of adaptive safety behaviors include wearing a seatbelt in the car, running out of the way in the face of an oncoming truck, and putting on protective gloves before removing a hot pan from the oven.

Engaging in safety behaviors becomes maladaptive, however, when they are used to protect against a perceived threat that exceeds the actual threat. These maladaptive safety behaviors, also called false safety behaviors, can be defined as "unnecessary actions taken to prevent, escape from, or reduce the severity of a perceived threat" (Telch & Lancaster, 2012; p. 315). For the purpose of brevity, the term "safety behavior" will be used to refer to maladaptive, or false, safety behaviors henceforward.

Safety behaviors are most commonly associated with anxiety disorders, but also emerge in other psychological disorders associated with exaggerated threat perception (e.g., fear of the consequences of not getting enough sleep in insomnia; Ree & Harvey, 2004). Correlational studies have demonstrated that higher anxiety is associated with more frequent safety behavior use (Cuming et al., 2009; Kamphuis & Telch, 1998; Rowa et al., 2015). More importantly, experimental studies have demonstrated that introducing safety behaviors increases anxiety in the related domain (Deacon & Maack, 2008;

Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011). Table 4 lists psychological disorders and associated examples of exaggerated threat and safety behaviors.

Table 4: Examples of false safety behaviors associated with exaggerated threat perception in DSM-V, Axis I disorders.

Disorder	Exaggerated Threat Examples	Safety Behavior Examples
Panic Disorder	Concern about dying from cardiac arrest because of a panic attack	-Eliminating all caffeine intake -Carrying an anxiolytic "rescue" medication at all times
Agoraphobia	Concern about embarrassing oneself if a panic attack occurs in a public place	-Avoiding leaving the house as much as possible -Brining a companion whenever leaving the house who could help in case of a panic attack
Social Anxiety Disorder	Concern that other people at a party will be likely to notice signs of anxiety and will be judgmental of it	-Going to the bathroom regularly to check for excessive sweating or blushing -Mentally reviewing the conversation afterwards to make sure there were no signs of nervousness
Generalized Anxiety Disorder	Concern about being fired from a stable job	-Checking with boss regularly to receive reassurance about adequate job performance -Continuous research on other job opportunities to prepare back-up options
Specific Phobia (Animal)	Concern about being attacked by an unprovoked dog while on a walk in the neighborhood	-Avoiding certain streets where dog owners live -Carrying a large stick to use as protection if attacked
Obsessive Compulsive Disorder	Concern about contracting a fatal illness when eating at a restaurant	-Using a paper towel to open doors -Cleaning with hand sanitizer after touching tables, chairs, and menus
Post-traumatic Stress Disorder	Concern about being assaulted when going shopping	-Carrying pepper spray at all times -Avoiding going out alone
Illness Anxiety Disorder	Concern about high probability of getting skin cancer	-Checking changes in moles by taking pictures every week -Extensively researching signs of skin cancer on the internet
Insomnia	Concern about loosing a job due to poor performance at work after sleep deprivation	-Eliminating all caffeine intake -Repeatedly checking the time before falling asleep to make certain that it is not too late to get enough sleep
Bulimia Nervosa	Concern about appearing overweight	-Avoidance of tight fitting clothing -Regularly checking mirrors and scales to monitor weight gain

THE INFLUENCE OF SAFETY BEHAVIORS ON EXPOSURE THERAPY: THEORETICAL DEVELOPMENTS

Negative Reinforcement and Conditioned Safety Signals

Mowrer's (1960) two factor learning theory was one of the first models to address safety behaviors in its discussion of avoidance and escape. The theory described how avoidance and escape are maintained by the rewarding experience of anxiety reduction. It furthermore suggests that avoidance and escape behaviors interfere with exposure to the conditioned stimulus, thereby preventing fear extinction.

Mowrer later added to this theory a "safety signal hypothesis" which was elaborated by Gray (1971), to describe the role of safety signals in maintaining anxiety. This modification to the theory suggests that certain stimuli become conditioned safety signals because they are associated with the non-occurrence of a predicted negative outcome. For example, the presence of a companion can become a signal of safety for someone with agoraphobia because the companion is associated with instances in which the patient was able to leave the home without the feared consequences. Therefore, the presence of the companion also serves to maintain the fear of leaving home.

Response Induction or Judicious Use

In line with these ideas, Rachman (1983; 1984) described how avoidance behavior is reduced in the presence of a safety signal (e.g., a companion or a talisman associated with safety, such as an anxiolytic medication), and proposed the possibility of using safety signals therapeutically. Specifically, he suggested facilitating approach behaviors by placing safety signals within the feared environment, so that the agoraphobic individual would need to enter the feared situation to approach the safety signal. Rachman (1983) predicted that, although the safety signals would be temporarily reinforced, their presence would increase approach behavior towards feared situations,

which would result in decreases in physiological anxiety responses and subjective fear, which would, in turn, eventually produce the effect of decreasing dependency on the safety signal. Put simply, Rachman predicted that using safety behaviors therapeutically might facilitate, rather than interfere, with the process of exposure therapy.

Very much in line with his original ideas, Rachman and colleagues more recently provided an argument for the judicious use of safety behaviors in anxiety treatment (Rachman, Radomsky, & Shafran, 2008). The authors described studies in which safety behavior use did not interfere with threat disconfirmation or fear reduction in the context of exposure therapy, and in some cases, may have facilitated treatment outcomes (e.g., Bandura, Jeffery, & Wright, 1974; Rachman, Craske, Tallman, & Solyn, 1986). Based on his review of the literature, Rachman and colleagues (2008) suggest that safety behaviors should be used "in a limited manner and only for a limited period, especially in the early stages of treatment" and also "if an obstacle is encountered later in the course of treatment" (p. 171). These descriptions are reminiscent of the use of safety behaviors in Bandura's guided mastery treatment (Bandura, Jeffery, & Gajdos, 1975), in which response induction aids are used to induce approach behaviors and increase self-efficacy, and are then faded over time. Rachman and colleagues (2008) contrast the judicious use of safety behaviors to the approach used by cognitive therapists, whom he suggests, "often encourage patients to drop their safety behavior completely and as soon as possible" (p.164).

Threat Disconfirmation and Misattribution of Safety

Whereas Rachman's view highlights a potential therapeutic use of safety behaviors as response induction tools, cognitive theory, on the other hand, provides a heavier emphasis on the potential pitfalls of safety behavior use. In terms of treatment recommendations, Salkovskis and colleagues suggest that, "it is important to eliminate

any safety-seeking behaviors which may be maintaining catastrophic cognitions" (Salkovskis, Clark, & Gelder, 1996). Safety behaviors are seen as blocking threat disconfirmation because the experience of safety is misattributed to the use of the safety behaviors (Salkovskis, 1991; Telch, 1991). For instance, someone with a fear of heights might misattribute safety to his habit of tightly gripping the rails whenever he is in a high place, preventing him from receiving evidence that he is unlikely to fall even when not gripping the rails. Safety behaviors therefore are reinforced due to the perception that the predicted catastrophes are averted (Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999).

In line with threat disconfirmation theory, a systematic review of the safety behavior literature conduced by Goetz, Davine, Siwiev, and Lee (2016) concluded that preventive safety behaviors were more detrimental to exposure therapy than restorative safety behaviors. Preventive safety behaviors prevent full exposure to the threatening situation (e.g., wearing a glove while touching a perceived contaminated object), whereas restorative safety behaviors restore safety after unprotected exposure to the threatening situation (e.g., using a sanitary wipe after direct contact with an object perceived to the contaminated). In line with findings from Goetz et al. (2016), cognitive theory would predict that restorative safety behaviors would be less detrimental than preventive safety behaviors because restorative safety behaviors allow for full confrontation with the threatening situation, even if only for brief period of time prior to performance of the safety behavior. A limiting factor of the prior research in this area is that nearly all research on restorative safety behaviors has been conducted within populations typically associated with rituals used to reduce threat, most often OCD or health anxiety.

Reducing Attentional Resources

Telch and colleagues (Sloan & Telch, 2002; Telch & Lancaster, 2012) have suggested that SBs may interfere with exposure therapy by interfering with the processing of threat disconfirmation via a redirection of attentional resources to the presence of safety cues and the execution of safety behaviors. In support of this formulation, Telch and colleagues (Kamphuis & Telch, 2000; Telch et al., 2004) found that adding a heavy cognitive load task during exposure therapy for claustrophobia reduces treatment efficacy. Moreover, in three independent exposure therapy studies, Telch and colleagues (Kamphuis & Telch, 2000; Sloan & Telch, 2002; Telch et al, 2000) showed that experimental manipulations designed to explicitly increase attention to threat-disconfirming information enhance exposure treatment outcomes. These findings are consistent with emotional processing theory (Foa & Kozak, 1986), which underscores the importance of attending to the feared stimulus and threat-disconfirming information throughout treatment as a necessary precursor to emotional processing.

Threat Transmission Hypothesis

Telch and colleagues (Sloan & Telch, 2002; Telch & Lancaster, 2012) have also suggested the possibility of a non-cognitive model, in which the mere engagement in protective actions is hypothesized to transmit threat signaling via lower-level, limbic-type activation. In line with this idea, Niedenthal (2007) introduced the theory of embodied emotion suggesting that physical enactments consistent with a given emotion action tendency may lead to increased activation of the target emotion. Data supporting the threat transmission model comes from several more recent experiments demonstrating that having non-anxious populations engage in unnecessary protective actions is anxiogenic (Deacon & Maack, 2008; Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011).

Inhibitory Learning

Inhibitory learning theory similarly suggests the potential drawbacks of using safety behaviors. Inhibitory learning theory emerged from data in basic science models demonstrating that fear can re-emerge after extinction, and that this return of fear is more likely after a change in context, such as a change in environment (fear renewal) or even simply the passage of time (spontaneous recovery of fear; Bouton, 2000). It was therefore concluded that fear extinction procedures result in the formation of a new, context-dependent safety memory that competes with the original fear memory for expression. It follows, then, that exposure therapy should be more effective when the generalizability of the inhibitory memory is maximized. Blakely and Abramowitz (2016) integrated the long-standing debate on the therapeutic use of safety behaviors with the emergence of inhibitory learning theory to provide specific recommendations. They suggest that clinicians should perform a careful functional analysis of safety behaviors, and eliminate any safety behaviors that might reduce the generalizability of the inhibitory memory, reduce the discrepancy between anticipated and actual outcomes during exposure therapy, or reduce acquisition of distress tolerance skills during exposure therapy. The latter two recommendations are essentially strategies that fit under the umbrella of the first recommendation, to maximize the generalizability of the inhibitory memory. According to the definition of safety behaviors proposed by Telch and Lancaster (2012), any safety behavior would then have detrimental effects; when safety behaviors are defined as actions taken to "prevent, escape from, or reduce the severity of a perceived threat," every safety behavior would reduce the discrepancy between the anticipated and actual outcome.

PRIOR RESEARCH SYNTHESES

The theoretical discussion regarding the impact of safety behaviors has been ongoing for many years, and several qualitative reviews of the data on this topic have been published within in the last decade (Blakey & Abramowitz, 2016; Goetz, Davine, Siwiev, & Lee, 2016; Helbig-Lang & Petermann, 2010; Parrish, Radomsky, & Dugas, 2008; Rachman et al., 2008). Based on experimental data, some psychologists have tentatively suggested the potential benefits of judicious safety behavior use (Parrish, Radomsky, & Dugas, 2008; Rachman et al., 2008), whereas others have generally cautioned against their use (Blakey & Abramowitz, 2016; Helbig-Lang & Petermann, 2010; Sloan & Telch, 2002; Powers et al., 2004). Given the long-standing debate and numerous qualitative syntheses of the data, it is surprising that only one quantitative synthesis of the research in this area has been conducted to date (Meulders, Van Daele, Volders, & Vlaeyen, 2016).

Meulders and colleagues (2016) completed two separate meta-analyses investigating (a) the impact of adding safety behaviors, and (b) the impact of removing safety behaviors, as compared with a baseline/control condition (for example, a group with no instructions regarding safety behaviors). Authors identified a marginally significant effect in favor of removing of safety behaviors relative to a baseline control group, and no statistically significant effect of the addition of safety behaviors relative to a baseline control group. Overall they described their findings as "inconclusive," and stated that they "could not provide strong evidence support either the removal of addition of [safety behaviors] during exposure-based treatment" (p. 151). They also observed moderate to high heterogeneity in effect sizes, highlighting the inconsistency of results across studies included in their analysis. This heterogeneity in effect sizes may be in part related to the inclusion of studies that varied widely in their methodological rigor. When

one averages across studies of varying methodological rigor, the average true effect size of the manipulation may be diluted due to the reduced power of some studies to accurately measure the true effect of the manipulation.

For example, authors did not account for whether studies equated treatment conditions for safety behavior use/availability at the time of assessment. In some studies, for example, researchers compare fear ratings at the end of an intervention, while one group is using safety behaviors and the other is not (e.g., Langer & Rodebaugh, 2013). Other studies, in contrast, conduct a separate assessment after the treatment manipulation, during which neither group has access to safety behaviors (e.g., Goetz & Lee, 2015). One might expect that using safety behaviors reduces fear in the short-run (while the safety behaviors are available), but increases fear in the long-run (when presumably safety behaviors may be less available; Mowrer, 1960; Salkovskis et al., 1996). Therefore, when safety behavior use/availability is not equated during the outcome assessment, one might expect lower fear in the group with access to safety behaviors. However, when both groups are tested under equivalent conditions (e.g., when neither has access to safety behaviors), one might then expect to detect higher fear in the group that had access to safety behaviors during treatment. Therefore, differences in effect sizes when testing conditions are and are not equivalent, in regard to safety behavior availability and use, could be a significant source of variability in study effect sizes.

Another potential drawback of Meulder's and colleagues (2016) approach was the inclusion of studies that used within-subjects designs (e.g., Wells et al., 1995). Although there are benefits of using more generous study inclusion criteria (e.g., increased statistical power), the use of within-subjects designs poses a critical methodological problem when studying the impact of safety behavior use on treatment outcome. Various theoretical perspectives on safety behaviors (e.g., threat disconfirmation, response

induction, and inhibitory learning) describe their long-term, learning-based influences. Therefore, using a within-subjects design to test the influence of a safety behavior manipulation poses the potential problem of carryover effects. These are effects that can carry over from the first phase of the study into the second, and thus obscure observation of the impact of an experimental manipulation in a within-subjects design (Wellek & Blettner, 2012). Therefore, excluding studies using a within subjects design may increase the ability to detect the true effect of safety behavior manipulations.

A third limitation of their findings relates to the relatively narrow search terms used by authors in their literature review. Meulders and colleagues (2016) narrowed their literature review by searching for studies that explicitly mentioned safety behaviors. The generalizability of findings could be increased by examining a broader array of studies in line with the approach taken prior authors of systematic reviews in this area (e.g., Goetz et al., 2016), who included studies that did not explicitly use the term "safety behavior" (e.g., distraction-related studies).

Finally, Meulders and colleagues (2016) noted the limitations of their methodology in selecting only one outcome measure to code per study, specifically, self-reported fear at the last available time point. Rather than selecting one primary effect to code for each study, it is possible to code all study outcomes and average across them to generate findings more generalizable across outcome measures (Cooper, 1998). This could strengthen the generalizability of conclusions, and produce the added benefit of allowing one to test moderators related to assessment type. It is also noteworthy that even with incorporating only one type of outcome measure, Meulders and colleagues (2016) still observed medium to high heterogeneity in effect sizes across studies. Therefore, in addition to testing potential moderators related to assessment characteristics, it may be useful to examine moderators related to study characteristics as well.

POTENTIAL EFFECT SIZE MODERATORS

Assessment Characteristics

It remains to be determined whether the characteristics of certain assessments make them more or less sensitive to detecting the influence of safety behavior manipulations on exposure therapy. For instance, assessment time point could influence effect sizes. If safety behavior use does indeed reduce the generalizability of learning as inhibitory learning theory would suggest (Blakely & Abramowitz, 2016), then follow-up tests conducted weeks to months after treatment would be predicted to show larger effect sizes relative to assessments conducted immediately after treatment. Furthermore, some aspects of anxiety (behavior performance, physiological response, or subjective ratings) could be relatively more or less sensitive to detecting the influence of safety behaviors on exposure therapy. Given the rooting of safety behavior manipulations in cognitively focused theories (e.g., threat disconfirmation), one might expect subjective ratings to demonstrate higher sensitivity to detecting the influence of safety behaviors relative to other assessment modalities.

Clinical Status and Treatment Target

Related to study design features, the impact of safety behaviors may also depend on the clinical status of the sample. Due to the potency of exposure therapy as a general treatment technique and potential for floor effects in non-clinical samples, one might expect to see a stronger influence of safety behaviors on exposure therapy outcomes as the clinical sample increases in severity (e.g., within diagnosed versus sub-threshold patients). Additionally, the impact of safety behaviors may depend on the psychological condition under investigation. Safety behaviors are often implemented to divert a specific threat. Therefore, one might expect to see a stronger influence of safety behaviors on circumscribed threat perceptions, such as specific phobias.

Safety Behavior Characteristics

Features of the safety behavior manipulation within a given study could also contribute to the relative strength or weakness of their influence on exposure therapy outcomes. For example, most studies investigating the influence of adding safety behaviors to exposure therapy conduct this manipulation by providing participants with a specific list of safety behaviors from which to choose (i.e., investigator-initiated safety behaviors). This type of safety behavior manipulation is limited in its ecological validity, since safety behaviors provided by investigators might not map onto the safety behaviors participants would use in a real-world scenario. Furthermore, investigator initiated safety behaviors may have a weaker influence on outcomes relative to safety behaviors that participants have used prior to study participation. The latter behaviors would likely have a stronger history as a conditioned safety signals, in turn making them more potent for blocking extinction learning (Rescorla, 1969).

Furthermore, the use of investigator-initiated safety behaviors poses limits to construct validity. It is possible that a given behavior that one individual views as increasing safety, another individual views as decreasing safety. The behavior of looking away from a spider, for example, could increase a sense of safety by allowing for distraction or experiential avoidance. However, this same behavior could also decrease a sense of safety by preventing hyper-vigilant watching of the spider's movement. Thus, the use of investigator-initiated safety behaviors, as opposed to safety behaviors selected by the participant, poses a number of methodological issues that could impact the integrity of the safety behavior manipulation.

Studies investigating the addition of safety behaviors to exposure therapy also differ on whether investigators require the use of these safety behaviors during treatment, or alternatively, simply allow, but do not require, performance of safety behaviors (for

examples of each type of manipulation, see Powers, Smits, & Telch, 2004; and Sy, Dixon, Lickel, Nelson, & Deacon, 2011). Individual studies have found no differences between these two treatment conditions (e.g., Powers et al., 2004; Sy et al., 2011). However, this feature of safety behavior manipulation has yet to be investigated as one that might explain variability in findings within the safety behavior literature more broadly.

STUDY AIMS

We therefore conducted a meta-analysis of the safety behavior literature, improving on limitations in prior research syntheses (Meulders et al., 2016), with the primary aim of investigating the impact of adding safety behaviors (SB+) and removing safety behaviors (SB-) on outcomes of exposure therapy. Our secondary aim was to examine potential moderators of effect sizes. This included evaluating the moderating influence of characteristics related to assessments, such as the modality of assessment, and duration of follow-up; and characteristics related to studies, such as the severity of the clinical population, the diagnostic target of treatment, and the characteristics of the safety behaviors manipulated.

Methods

Literature Search Procedures

We searched for published, peer-reviewed articles from 1909 to February 2015 in PsychINFO, Medline, PsychARTICLES, and the Psychology and Behavioral Sciences Collection. The search terms consisted of two domains of keywords: the first set of terms related to safety behaviors and the second set related to psychotherapy. The first term list included: safety behavior, safety behaviors, safety behaviour, safety behaviours, safety seeking, safety signal, safety signals, safety aid, safety aids, response prevention, ritual prevention, distraction, response aid, response aids, response induction aid, response induction aids, guided mastery, and participant modeling. The second term list included: treatment, therapy, psychotherapy, counseling, counselling, intervention, and exposure. All possible combinations of these two sets were searched for in the abstracts, titles, and subject terms. We then completed a backward literature review, reviewing the references from relevant review articles as well as the references in empirical studies selected for inclusion in the meta-analysis. After removing duplicates, this search process yielded a total of 2,228 unique records. Articles were then screened and selected according to specific inclusion/exclusion criteria (see below).

Study Inclusion/Exclusion Criteria

Studies were reviewed by one of three researchers (first, second, and third authors). Upon review of 100 randomly selected articles from the overall literature search, the authors demonstrated 100% agreement on decisions regarding study inclusion. All study reviewers were trained and supervised by the first author, who reviewed each study selected for inclusion a second time to ensure all studies met the inclusion criteria.

See Figure 2 for an overview of the study selection process. Each article was evaluated based on the following inclusion/exclusion criteria:

(1) Studies were required to provide an experimental (randomized) manipulation of safety behaviors in the context of subjects receiving exposure therapy.[2] Two major subtypes of SB manipulations were included: (a) studies which randomized subjects to an experimental condition that made safety behaviors/safety aids available for use (SB+) versus an exposure only control; and (b) studies which randomized subjects to an experimental condition that required subjects to eliminate their SBs during exposure (SB-) versus exposure control (i.e., allowing subjects to complete exposure therapy without SB elimination)

(2) Both the experimental and control groups had to receive equivalent forms of exposure therapy, defined as confronting a situation (in vivo), thought (imaginal), or bodily sensation (interoceptive) for the primary purpose of reducing symptoms of psychopathology. This criterion led to the exclusion of studies that compared distraction to focusing or mindfulness-based conditions.[3] In the context of our primary research questions, these studies would confound the impact of the safety behavior (distraction), with the potential facilitating effects of increasing attention and focus toward the symptom-provoking stimulus (Foa & Kozak, 1986). Instead, we only selected distraction studies that compared the impact of distraction to an exposure-only control group.

(3) Studies using crossover designs were excluded due to the potential for carry-over effects to obscure the effects of SB+ or SB- manipulations.

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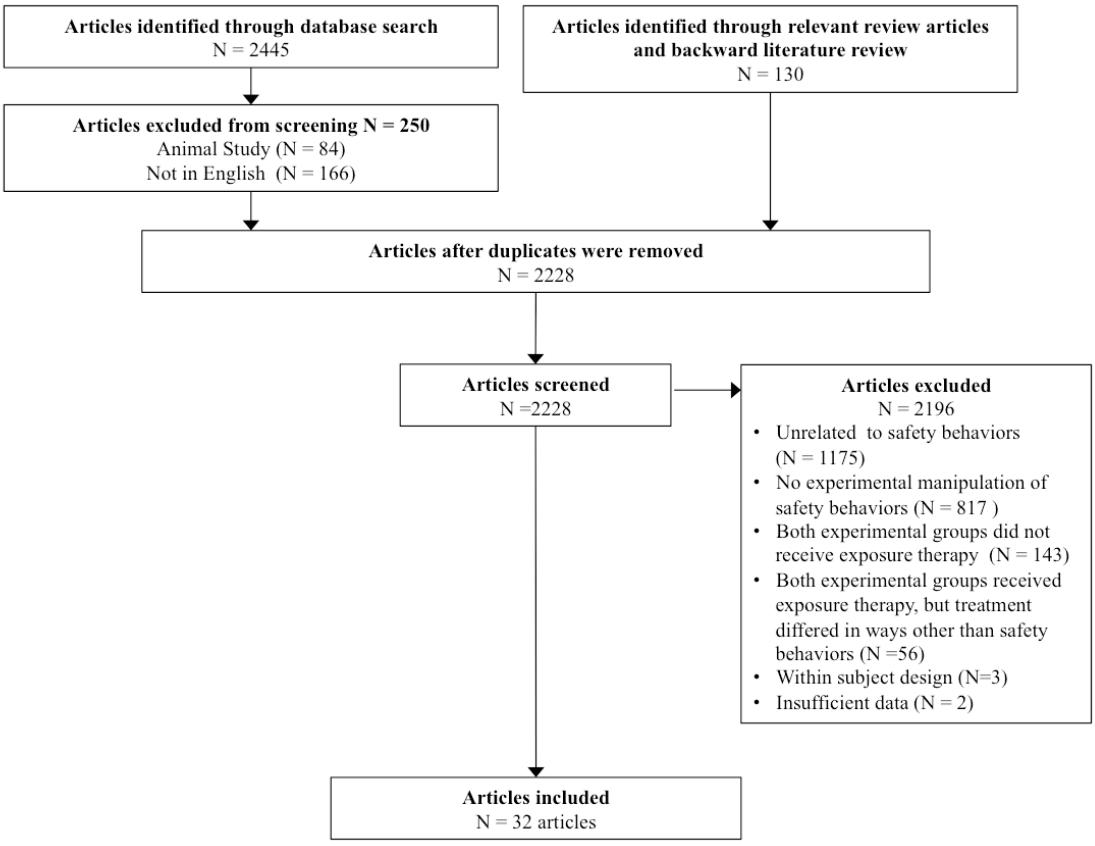
[2] We excluded complete avoidance of feared stimuli from the category of safety behaviors, because by this definition, all forms of exposure therapy would qualify as safety behavior reduction.

[3] The exclusion of conditions that added a mindfulness or focusing component to treatment was based on a careful review of the study procedures, rather than relying solely on labels for study conditions provided by authors.

(4) Studies were excluded if the article provided insufficient data to allow for the determination of between-group effect sizes.

Figure 2: Overview of study selection.



CODING PROCEDURES

A double data entry procedure was used. Two authors (first and second) independently coded each effect size, along with the characteristics associated with the type of outcome assessment, the nature of the clinical sample and diagnostic target of exposure therapy, as well as the characteristics related to the safety behavior manipulations within each study. Any disagreements in independent coding were resolved through discussion and unanimous agreement of both coders.

Assessment Characteristics

Each outcome assessment was coded as having either equivalent or non-equivalent safety behavior instructions during the assessment. For example, fear ratings provided at the end of treatment, while one group is using safety behaviors and the other is not, would be considered a non-equivalent comparison; whereas a behavioral avoidance test or questionnaire administered after treatment, during which there were no between-group differences in safety behavior use or availability, would be considered an equivalent testing condition.

Each outcome was additionally coded for follow up duration, specifically, the number of days since treatment completion. Outcomes that were assessed at the end of treatment or on the same day that treatment was completed were coded as "end of treatment" or "post treatment" measures, respectively (0 days); and all other outcomes were coded as "follow-up" assessments. Finally, we coded the modality of outcome indices. All reported outcome indices were first subdivided into two broad assessment categories – (1) symptom questionnaires, or (2) behavioral approach tests (BATs) – defined as assessments obtained while the participant directly encounters a fear-provoking target. BAT indices were further subdivided into measurements of observed approach behavior, subjective ratings of experience (e.g., Likert ratings of anticipated or peak fear/distress), and physiological reactivity (e.g., heart-rate or electrodermal responding) during the encounter.

Coding of Sample and Treatment Target Characteristics

The clinical status of the sample was categorized as (a) meeting diagnostic criteria for the psychopathological condition targeted for treatment; (b) "symptomatic," defined as a sample displaying elevated symptom levels for the psychopathological condition targeted for treatment; or (c) "general sample," defined as a sample recruited from the

general population without screening for symptom level or diagnostic status. Studies were furthermore categorized according to the diagnostic condition targeted by exposure therapy. For example, exposure therapy aimed at reducing cleaning rituals in response to germ exposure was coded as treatment for OCD symptoms, whereas exposure therapy fear of spiders or enclosed spaces was coded as treatment for specific phobia symptoms.

Coding of Safety Behavior Characteristics

Coders additionally categorized studies by the nature of the safety behavior manipulation. First, studies were subdivided into those that tested exposure therapy with and without the addition of safety behaviors (SB+ studies); and those that tested exposure therapy with and without the removal of safety behaviors (SB- studies; Meulders et al., 2016). Due to differences in the study designs, the interpretation of effect sizes for each of these two study subgroups differs. Therefore, averaging across them would produce effect size estimates that would be difficult to interpret.

The remaining safety behavior characteristics were used for the purpose of moderator tests. Studies were categorized regarding whether or not they focused solely on the manipulation of distraction. Although a prior meta-analysis included distraction in the conceptualization of safety behaviors, authors did not use distraction as a search term in the literature review (Meulders et al., 2016). Since the present study included this as a search term, many additional articles related to distraction were included. We therefore decided to examine whether the impact of simply manipulating distraction differed from the impact of manipulating other subtypes of safety behaviors (more representative of the safety behaviors included in a prior research syntheses; Meulders et al., 2016).

We furthermore categorized studies regarding whether or not safety behavior use was required. For example, in the study designs of Powers and colleagues (2004) and Sy and colleagues (2011), authors exposed participants to a claustrophobia chamber; in one

condition, experimenters made safety behaviors available without requiring their use, and in another condition, experimenters required the use of one or more safety behaviors during exposure therapy. The former condition was coded as safety behaviors "not required," whereas the latter condition was coded as safety behaviors "required."

Finally, studies were categorized into those involving safety behaviors that were suggested or selected by the investigator ("investigator initiated" safety behaviors) versus safety behaviors that were selected by the participant ("naturally occurring" safety behaviors). When participants were provided with suggestions for safety behaviors from the investigator, but were also allowed to add safety behaviors of their preference, the study was categorized as manipulating "naturally occurring" safety behaviors. This ensures that the categorization delineates groups with more versus less tailoring of safety behaviors toward actions that the individual participant views as increasing a sense of safety.

Studies testing the removal of safety behaviors from exposure therapy (SB- studies) exhibited the same safety behavior characteristics across all studies, so were not tested for moderation related to safety behavior characteristics. For example, no studies in the SB- group manipulated only distraction because participants were encouraged to fade a broader range of safety behaviors in these study designs. Furthermore, all studies manipulated naturally occurring, rather than investigator initiated safety behaviors, since the unique safety behaviors each participant presented with were removed during treatment. The categorization of "required" versus "not required" use of safety behaviors also was not relevant to this study design because no safety behaviors were introduced. Therefore moderator testing of safety behavior characteristics was conducted within the SB+ studies only.

Effect Size Coding

We coded effect sizes that represented outcome measures (not process or mid-treatment assessments) for each study because our primary aim was to evaluate the impact of safety behaviors on treatment outcomes rather than treatment process. All included effect sizes therefore reflect assessments collected at the end of treatment or at a later follow-up date. Furthermore, effect sizes included in the analysis were all directly related to the psychological condition being targeted during the exposure-based therapy. Examples of effect sizes that were unrelated to the condition being targeted during exposure therapy include a subjective rating of "enjoyment of the experiment" and a depression questionnaire within studies targeting anxiety reduction. (Only 17 out of over 200 data points were excluded due to being unrelated related to the primary condition being targeted by treatment.)

To avoid over-weighting or double-counting of a single outcome assessment, whenever one outcome measure was presented in two separate forms by study authors, we selected the version of the outcome measure that was more sensitive to change, and the version that was more inclusive. For example, if study authors examined questionnaire outcomes both continuously (total score) and categorically (reached a cutoff or not), we selected the continuous measurement. When a questionnaire total was provided alongside all subscales in the measure, we selected the subscales for analysis, due to the potential for better sensitivity to change related to the presumably higher internal consistency within each subscale. However, when outcomes for one item within a questionnaire were presented alongside the questionnaire total score, we entered the more inclusive version of the measure (i.e., the questionnaire total score) to avoid loss of information.

Each effect size was coded in the direction reported in the original manuscript, and then categorized as to whether higher or lower scores represented greater psychological symptoms. Prior to analyses, the direction of effect sizes was then reversed when needed such that higher scores on assessments would uniformly represent higher symptom levels. Outcome effect sizes were then adjusted for pre-treatment levels by subtracting mean pre-treatment scores (when available) from mean post-treatment scores, within each of the two treatment groups in the comparison.

To evaluate the impact of the safety behavior manipulation, we calculated the difference in the adjusted outcome scores between the two treatment groups. For ease of interpretation, the group with more safety behaviors was consistently placed first in the subtraction calculation (more safety behaviors minus less safety behaviors). For the SB+ studies, the group with safety behaviors added was listed first. For the SB- studies, the group without safety behavior fading was listed first. This series of calculations ensured that positive effect sizes in both SB+ and SB- studies could be interpreted as lower safety behavior use producing superior treatment outcomes.

To maximize precision of the effect size calculations, we used means, standard deviations, and sample size for continuous variables (or probability of a given outcome, for dichotomous variables), whenever these data were available. When these data were not available, we derived effect sizes from statistical calculations (e.g., *F*-values or *t*-values) using formulas recommended by Lipsey and Wilson (2001). When none of these data were available, effect sizes were estimated based on reported *p*-values.

DATA ANALYSIS

Effect sizes were calculated as Hedges' *g* (Hedges & Olkin, 1984) since this formula is less biased than Cohen's *d* for small sample sizes, which were prevalent among the studies in the present analysis (Table 5). Both *g* and *d* reflect the difference

between means in units of pooled standard deviation. However, the pooled standard deviation for Hedges' *g* uses Bessel's correction ((*n*-degrees freedom) rather than (*n*)) for calculating the pooled standard deviation, and it weights each standard deviation in the pooled calculation with its respective sample size. Although as sample sizes increase, Hedges' *g* converges with Cohen's *d*, among smaller sample sizes this correction protects against an upwardly biased estimate of effect size (Grissom & Kim, 2005). To adjust the post-treatment effect size for pre-treatment levels (when these data were available), we followed recommendations provided by Morris (2008). Pre-post change in each group was calculated by subtracting pre-treatment scores from post-treatment scores. Then, the mean pre-post change in the first treatment group (with more safety behavior use) was subtracted from the mean pre-post change in the second treatment group (with less safety behavior use), which was divided by the pooled and weighted pretest standard deviation. We then calculated 95% confidence intervals for weighted average effect sizes, and rejected the null hypothesis when the confidence interval did not contain zero.

Correcting for Dependence Among Effect Sizes

Following the assumption of the independence of each effect size can be problematic when the same sample of participants produces multiple effect sizes for a given study. A common occurrence of this violation was when multiple outcome measures were used for a given sample. We therefore used a shifting units of analysis approach to statistically account for dependent effect sizes (Cooper, 1998). Consistent with this methodology, we entered all available treatment outcome effects associated with each sample, and coded each in accordance with their associated study and assessment characteristics. An overall effect size was calculated by averaging across all available effect sizes for a given sample. When examining the influence of moderators related to

subcategories of effect sizes, a given sample could contribute one effect size to each level of the moderator variable.

Occasionally study design created another type of effect size dependence, such that the same treatment group was used in two unique between-group comparisons. In these cases, the sample size of the group used in both comparisons was halved to correct statistically for the problem of dependence among effect sizes. For example, some studies compared a standard exposure therapy control group with two experimental groups (one that required the use of safety behaviors, and one that made safety behaviors available but did not require their use; Powers et al., 2004; Sy et al., 2011). In this case, we coded the two unique between-group comparisons for each of the two experimental groups as compared with the exposure-only control group, and we halved the sample size of the control group in each comparison. We selected this option (halving the sample size of the control group rather than averaging across the two experimental groups) because this enabled us to test moderating effects associated with the various pairwise comparisons (e.g., differing impact of adding safety behaviors during exposure therapy when their use is required as compared to when it is not required).

Fixed Versus Random Models

After calculating Hedges' *g*, we used both fixed and random effect models to examine the average overall effect of safety behaviors (adding or removing them) on exposure therapy outcomes. Due to low sample sizes and statistical power limitations, as well as the exploratory nature of the moderator analyses, we only used fixed effect models in the subsequent moderator analyses (see Qualitative Coding section a description of tested moderators). Fixed effects models assume that the source of error in the estimated effect size is due to sampling error associated with selecting a subset of studies from a single population of studies; whereas random effects models assume both

(a) sampling error associated with selecting a subset of studies from a single population of studies, and (b) sampling error associated with selecting a subpopulation of studies from super-population of studies (Field & Gillett, 2010). Although one could argue that random effects models produce findings that are more generalizable to studies outside the sample included in our paper, we selected fixed effects models for moderator analyses to maximize statistical sensitivity to detect moderator effects that may help to guide future research in this area.

Moderator Tests

Systematic differences in the characteristics of studies can contribute to the variance in their effect sizes, over and above sampling error alone. We used a goodness of fit test to determine whether the level of heterogeneity observed within effect sizes (*Qw*) was greater than what would be expected from sampling error alone. When the effect sizes were heterogeneous (as indicated by a statistically significant *Qw*), we performed further moderator tests to determine whether factors such as study characteristics explained variance in the effect sizes (Cooper, Hedges, & Valentine, 2009). The predictive utility of each moderator was examined by testing whether the variance between groups of effect sizes (*Qb*) was greater than what would be expected from sampling error alone.

Sequence of Analyses

For the SB+ and SB- groups, we first conducted preliminary tests, which included (a) determining whether equivalence of testing conditions moderated the effect, and excluding non-equivalent tests in further analyses if indicated, and (b) examining the heterogeneity of the remaining effects. We then calculated fixed and random effects for the overall impact of adding and removing safety behaviors, relative to an exposure

therapy control group. Last, we reported fixed effects for moderator tests of assessment, study, and safety behavior characteristics, when this testing was indicated by significant heterogeneity in the effect sizes.

Results

The literature review yielded a total of 32 articles, with 47 unique between-group comparisons. See Table 5 for a summary of the characteristics of each study. Among the studies that experimentally manipulated the addition of safety behaviors to exposure therapy (see Table 6), there were 42 between-group comparisons, which yielded a total of 183 effect sizes. Among the studies that experimentally manipulated the removal of safety behaviors during exposure therapy (see Table 7), there were 5 unique between-group comparisons, which yielded a total of 26 effect sizes.

Table 5: Description of general study characteristics for included studies.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Abramowitz & Moore, 2007	Hypochondriasis	27	Diagnosed	Effects of SB's (e.g., checking) on anxiety when exposed to personally-relevant health related stimuli.	SB's reduced anxiety and urge to perform SB's. For patients in the no SB condition, a more gradual reduction in anxiety and urge to perform SB's was observed. → SB's serve the function of immediately reducing anxiety. However, reductions in anxiety can also occur after 1 hour of refraining from SB use.
Antony et al., 2001	Specific Phobia	60	Diagnosed	Effects of distraction and coping style on exposure-based treatment	Neither distraction, coping style, nor their interaction had a significant effect on outcomes. →Distraction does not produce an inhibitory effect on fear reduction in the short-term.
Deacon et al., 2010	Specific Phobia	33	Symptomatic	Judicious use of SB in augmenting exposure therapy tolerability	Equivalent improvements for both groups. No reliable benefits or drawbacks associated with judicious use of SB's. → SB use during exposure therapy may not compromise therapy.
Eifert & Heffner, 2003	Panic Disorder	40	Symptomatic	Effects of control context (diaphragmatic breathing) on avoidance of aversive interoceptive cues	Subjects in the control context condition (diaphragmatic breathing) did not differ significantly from the no instruction group on measures of cognitive, physiological, and experienced fear symptoms or on frequency of catastrophic thoughts. → Diaphragmatic breathing does not provide an anxiolytic benefit in response to aversive interoceptive stimulation.

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Goetz & Lee, 2015	OCD	67	General sample	Effects of preventive and restorative SB's on exposure therapy	The restorative SB group experienced greater reductions in fear and behavioral avoidance relative to the preventive SB group. The restorative SB group and no SB group experienced equivalent reductions in fear. The restorative SB group experienced greater reductions in behavioral avoidance relative to the no SB group. →Restorative SB's facilitate exposure therapy and preventive SB's impair therapeutic gains
Hadjistavropoulos et al., 2000	Chronic Pain	30	Symptomatic	Effects of health anxiety and coping strategies on response to physical therapy	Coping strategy use had a minimal impact on response to physical therapy (when ignoring moderating effects of health anxiety levels). →Distraction is a better strategy for non-health anxious patients. Distraction produced greater affective pain, and worry about injury for health anxious patients than for non-health anxious patients.
Haw & Dickerson, 1998	Specific Phobia	72	Symptomatic	Effects of distraction on desensitization and reprocessing of aversive information	All groups experienced equivalent reductions in self-report and heart rate indices of anxiety. At follow-up, distraction groups displayed increased anxiety relative to the control group. →Distraction does not improve desensitization and reprocessing of aversive information
Hood et al., 2010	Specific Phobia	43	Symptomatic	Effects of SB's on behavioral, cognitive, and subjective measures of fear during exposure therapy	Both groups evidenced comparable reductions in self-reported anxiety and negative beliefs about spiders at post-treatment and follow-up. → Results challenge the notion that SB's are always detrimental to the efficacy of exposure therapy

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Kamphius & Telch, 2000	Specific Phobia	28	Symptomatic	Test predictions from emotional processing theory of fear reduction	Cognitive load task had a detrimental effect on fear reduction. →Fear reduction is hampered by distractions that are cognitively demanding
Kim, 2005	Social Anxiety	45	Symptomatic	Effects of decreased SB's on social anxiety and negative thoughts	Exposure with decreased SB's under cognitive rationale produced the greatest reductions in anxiety and negative beliefs. Both exposure with decreased SB's/cognitive rationale and exposure with decreased SB's/extinction rationale outperformed exposure with no decrease in SB's. →SB's negatively impact exposure therapy
Kircanski et al., 2012	Specific Phobia	44	Symptomatic	Effects of distraction during exposure on fear responding	The distraction and exposure alone groups did not differ on skin conductance response change →Distraction did not have a detrimental effect on exposure compared to exposure alone.
Levitt et al., 2004	Panic Disorder	28	Diagnosed	Effects of emotion regulation strategies during biological challenge	No differences were found between the suppression group and the control group on any measures. →Suppressing emotions as a coping strategy does not necessarily increase anxiety relative to no instructions. However, it is possible that in this clinical sample patients in the control group naturally engaged in emotional suppression.
Milosevic & Radomsky, 2008	Specific Phobia	62	Symptomatic	Examine effects of SB's on exposure treatment	The safety behavior use group and the no safety behavior group experienced comparable treatment gains. →Safety behaviors may not interfere with exposure therapy.

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Milosevic & Radomsky, 2013	Specific Phobia	126	Symptomatic	Effects of SB's on belief change during behavioral experiment	Negative beliefs decreased more in the safety behavior group relative to the no safety behavior group. →Safety behavior may enhance cognitive-behavioral therapy.
Morgan & Raffle, 1999	Social Anxiety	30	Diagnosed	Effects of dropping SB's during group exposure therapy	The group with instructions to drop SB's evidenced greater treatment gains on measures specific to social anxiety relative to the control. →Instructions to drop SB's may improve the efficacy of exposure tasks during CBT
Oliver & Page, 2003	Specific Phobia	32	Symptomatic	Replicate previous findings where distraction enhanced within-session fear reduction during exposure	Exposure plus distraction produced the most fear reduction within-session, between-session, at posttreatment, and at follow-up. →Distraction improves exposure treatment
Oliver & Page, 2008	Specific Phobia	30	Symptomatic	Effects of distraction on fear reduction during exposure	Subjects in the distraction groups reported the greatest fear reduction. →Distraction improves fear reduction within and between exposure sessions.
Penfold & Page, 1999	Specific Phobia	26	Symptomatic	Effects of distraction on fear reduction during exposure	Exposure plus distraction produced the greatest anxiety reduction within session. →Distraction may improve fear reduction during exposure.
Powers et al., 2004	Specific Phobia	44	Symptomatic	Investigate effects of perceived availability of SB's on fear reduction during exposure therapy	Exposure only achieved the highest end state functioning relative to exposure with SB's available and exposure with SB utilization. SB availability vs SB utilization experienced comparable end state levels of functioning. → The perception of available safety aids exerts a deleterious effect on fear reduction.

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Rachman et al., 2011	OCD	80	General sample	Effects of the judicious use of SB's during exposure therapy	Significant reductions in fear, disgust, and danger were experienced by both the ERP and exposure plus SB group. →SB's do not impair treatment gains.
Rodriguez & Craske, 1995	Specific Phobia	58	Symptomatic	Effects of distraction on fear reduction during exposure	Distraction produced a detrimental effect on fear reduction in the high intensity exposure group only. Distraction had no impact on fear reduction in the low intensity exposure group. →Distraction is more likely to negatively impact exposure when the intensity of the exposure is high.
Salkovskis et al., 2006	Panic Disorder	16	Diagnosed	Effects of dropping SB's on exposure therapy outcomes	Subjects who dropped SB's improved significantly on self-report measures of anxiety, panic, and avoidance and completed more steps on a behavioral walk task →Instructions to drop SB's may improve exposure therapy.
Sloan & Telch, 2002	Specific Phobia	29	Symptomatic	Examined effects of SB's on fear reduction during exposure therapy	Exposure with SB's achieved a lower state of clinically significant change at posttreatment and follow-up relative to exposure alone →SB's exert a detrimental effect on exposure therapy.
Sy et al., 2011	Specific Phobia	58	Symptomatic	Attempted to replicate deleterious effects of SB's from Powers et al., 2004	Subjects in all groups improved substantially and no between group differences were found in respect to fear reduction. →SB's may not have a deleterious effect on exposure therapy.

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
Taylor & Alden, 2010 (Study 1)	Social Anxiety	50	Symptomatic	Effects of SB's on exposure therapy and social judgements	Subjects in the exposure plus SB reduction group were less negative and made more accurate in their judgments of their performance. →Reducing SB's may help to alleviate social anxiety.
Taylor & Alden, 2010 (Study 2)	Social Anxiety	80	Diagnosed	Effects of SB's on exposure therapy and social judgements	Subjects in the exposure plus SB reduction group were less negative and made more accurate in their judgments of their performance. →Reducing SB's may help to alleviate social anxiety.
Taylor & Alden, 2011 (same sample as Taylor & Alden, 2010, Study 2)	Social Anxiety	80	Diagnosed	Effects of SB's on exposure therapy and social judgements	Subjects in the exposure plus SB reduction group exhibited increased perceived and actual positive interpersonal outcomes. →Reducing SB's may help to alleviate social anxiety by enhancing social approach behavior.
Telch et al., 2004	Specific Phobia	45	Symptomatic	Effects of high and low cognitive load distraction during exposure therapy	Subjects in the exposure only group evidenced the highest end sate functioning relative to exposure with low or high cognitive load distraction. Exposure with high cognitive load distraction achieved the lowest end state functioning →High cognitive load distractions can impair emotional processing during exposure therapy.
van den Hout et al., 2001	OCD	79	General sample	Effects of neutralizing an obsessive thought on anxiety	Immediate neutralization was accompanied by a steep reduction in anxiety. However, the no neutralizing group also experienced reductions in anxiety after 20 minutes. →Neutralization functions to reduce anxiety in response to obsessive thoughts.

Table 5, cont.

Author (s) & Publication Year	Type of Fear	N	Clinical Status	Study Focus	Findings & Conclusions
van den Hout et al., 2002	OCD	120	General sample	Effects of neutralizing an obsessive thought on anxiety	Within 2 minutes anxiety decreased to near baseline levels for all groups. →Anxiety in response to an obsession reduces over time regardless of whether neutralization occurred
van den Hout et al., 2011	OCD	29	Symptomatic	Conduct an extended replication of Rachman et al., (2011)	Findings were replicated. Both exposure alone and exposure with SB's produced marked declines in feelings of contamination, fear, danger, and disgust. →The use of SB's during exposure therapy should not be ruled out.
van den Hout et al., 2012	OCD	32	Symptomatic	Examined the effects of SB's on commitment to engage in exposure trails during therapy	SB's facilitated feelings of control over emotions relative to no SB's during exposure. →SB's may have beneficial effects of exposure therapy

**Note*. Salkovskis et al., 2006 used the same sample as Salkovskis et al., 1999. To avoid data dependency due to the shared sample, data were used from the final endpoint in Salkovskis et al., 2006.

Table 6: Description of relevant design features for safety behaviors added studies.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distra-ction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Abramowitz & Moore, 2007	Exposure to one idiosyncratic illness preoccupation trigger	Idiosyncratic behavior identified during interview with participant	No	Required	Naturally occurring	Maintained	No	BAT-Subjective	Baseline, End Treatment
Antony et al., 2001	120 minutes of hierarchical exposure to spider combined with modeling	Listened to educational audiocassette on world geography for the first hour of exposure	Yes	Required	Investigator initiated	Faded	Yes	BAT-Physio, BAT-Approach, BAT-Subjective, Questionnaire	Baseline, Posttreatment
Deacon et al., 2010	Graduated exposure in claustrophobia chamber. 6, 5-minute trials.	Three coping aids available: a) opening door on side of the chamber that faced a small fan blowing in fresh air, b) communicating with the experimenter via 2-way radio, c) having experimenter unlatch top of the chamber for the duration of the trial	No	Not Required	Investigator initiated	Faded	Yes	BAT-Subjective, Questionnaire	Baseline, Posttreatment, Follow-up (7 days)
Eifert & Heffner, 2003	Two, 10-minute 10% CO2 challenges	Diaphragmatic breathing taught before CO2 administration to gain control over symptoms during CO2 administration.	No	Required	Investigator Initiated	Maintained	both	BAT-Subjective, BAT-Approach	Baseline, End Treatment, Posttreatment, Follow-up (28 days)
Goetz & Lee, 2015	Touching an object perceived to be contaminated 15 times	Restorative SB group: Hand sanitizer use after touching contaminated object Preventive SB group: Using tissue to avoid contact with contaminated object	No	Required	Investigator Initiated	Maintained	Yes	BAT-Subjective, BAT-Approach	Baseline, Posttreatment

Table 6, cont.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distra-ction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Hadjistavropoulos et al., 2000	45 min active physiotherapy session (physical therapy for chronic pain patients)	Participants told to distract and avoid monitoring physical sensations (i.e., think of anything other than physical sensations during the sessions by using distraction)	Yes	Required	Investigator Initiated	Maintained	Yes	Questionnaire	Baseline, Posttreatment
Haw & Dickerson, 1998	6, 30-second exposures to a picture of a black widow spider on a computer screen	Distractions (either (a) following a dot, (b) reading a word, (c) following and reading a word)	Yes	Required	Investigator Initiated	Maintained	No	BAT-Physio, BAT-Subjective	Baseline, End treatment
Hood et al., 2010	35 minutes of graduated exposure to tarantula	Idiosyncratic -selected from author-generated list or suggested by participant	No	Required	Either	Maintained	Yes	BAT-Approach, Questionnaire	Baseline, Posttreatment, Follow-up (7 days)
Kamphius & Telch, 2000	Six, 5-minute trials of exposure to tightly enclosed hallway	Cognitive Load task- depressed button when three consecutive odd or even numbers were heard in their headphones, and added last two numbers whenever they heard a clicking noise	Yes	Required	Investigator initiated	Maintained	Yes	BAT-Physio, BAT-Subjective	Bassline, Posttreatment, Follow-up (14 days)
Kircanski et al., 2012	10 exposure trials of 38 seconds each sitting near a tarantula in a tank - same procedure repeated twice across two days	Create and speak a sentence including an object or piece of furniture found in their home and a room or location in which the furnishing is found	Yes	Required	Investigator initiated	Maintained	Yes	BAT-Physio, BAT-Approach, BAT-Subjective	Baseline, Posttreatment, Follow-up (7 days)
Levitt et al., 2004	15-minute inhalation of 5.5% CO2 enriched air	Listened to audiotape instructions prior to exposure instructing participants to suppress anxious thoughts and feelings and other discomfort	No	Required	Investigator initiated	Maintained	No	BAT-Physio, BAT-Subjective, Questionnaire	Baseline, End treatment, Posttreatment

Table 6, cont.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distra-ction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Milosevic & Radomsky, 2008	45 minutes graduated in vivo exposure to snake	Use of one or more response induction aids (parts of a bee keeper suit) when approaching snake	No	Not required	Investigator initiated	Maintained	Both	BAT-Subjective, BAT-Approach, Questionnaire	Baseline, End treatment, Posttreatment
Milosevic & Radomsky, 2013	20-minute self-paced behavioral experiment confronting a spider	Use of one or more response induction aids (parts of a bee keeper suit) when approaching spider	No	Required	Investigator initiated	Maintained	Both	BAT-Subjective, BAT-Approach, Questionnaire	Baseline, End treatment, Posttreatment
Oliver & Page, 2003	Three weekly 10-minute exposures to stimuli related to blood injection fears (two images with bloody wounds and a syringe filled with stage blood)	Engage in conversation with the experimenter that is unrelated to the exposure	Yes	Required	Investigator initiated	Maintained	Yes	BAT-Subjective, Questionnaire	Baseline, Posttreatment, Follow-up (30 days)
Oliver & Page, 2008	Three weekly 10-minute exposures to stimuli related to blood injection fears (two images with bloody wounds and a syringe filled with stage blood)	External focus group: conversation with the experimenter that is unrelated to the exposure Internal focus group: conversation with the experimenter that is unrelated to feared stimuli and focused on "aspects of the internal environment" (e.g. 'tell me how your feet feel in your shoes right now')	Yes	Required	Investigator initiated	Maintained	Yes	Questionnaire	Baseline, Posttreatment, Follow-up (30 days)

Table 6, cont.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distra-ction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Penfold & Page, 1999	Exposure to blood injury injection stimuli (images and syringe)	Exposure irrelevant conversation with experimenter	Yes	Required	Investigator initiated	Maintained	No	BAT-Subjective	Baseline, End treatment
Powers et al., 2004	30 minutes of in vivo exposure in claustrophobia chamber (6, 5-minute trials)	SB available group: Told three safety aids would be available, but only use them if you must: (a) opening a small window in the chamber to allow access to fresh air blown in by a small fan (b) unlocking the door after 2 minutes of exposure, c) communicating with experimenter via 2-way radio SB utilization group: Expected to use at least one of the above mentioned SB's during exposure	No	SB available group: Not required SB utilization group: Required	Investigator initiated	Maintained	Yes	BAT-Subjective, Questionnaire	Baseline, Posttreatment, Follow-up (14 days)
Rachman et al., 2011	Touching a selected contaminant 20 times during visit 1 and 16 times during visit 2. Contaminant used was one of 6 that elicited highest feelings of contamination at baseline.	Wiping with a hygienic wipe until feelings of contamination are reduced to 20% or lower. Immediately after exposure for the first 10 trials in visit 1, and after a 30 second delay after the second 10 trials in visit 1 and during visit 2.	No	Required	Investigator initiated	Maintained	No	BAT-Subjective	Baseline, End treatment
Rodriguez & Craske, 1995	Approached feared animal until fear is 70-80 on a 100-point scale (high intensity group) or 40-50 (low intensity group) and remain for 15-minutes	Instructions to look at slides while confronting animal	Yes	Required	Investigator initiated	Maintained	Yes	BAT-Physio, BAT-Subjective, BAT-Approach	Baseline, End treatment, Posttreatment

Table 6, cont.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distraction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Sloan & Telch, 2002	Six, 5-minute exposure trials in a claustrophobia chamber	SBs were optional but could be used if felt the need; a) opening window in chamber, b) standing near chamber door, c) checking door latch, d) talking with experimenter on intercom	No	Not Required	Investigator initiated	Maintained	Yes	BAT-Physio, BAT-Subjective, Questionnaire	Baseline, Posttreatment, Follow-up (14 days)
Sy et al., 2011	Up to 30 minutes of in vivo exposure in claustrophobia chamber (6, 5-minute trials)	SB available group: Told three safety aids would be available, but only use them if you must: (a) opening a small window in the chamber to allow access to fresh air blown in by a small fan (b) unlocking the door after 2 minutes of exposure, c) communicating with experimenter via 2-way radio SB utilization group: Expected to use at least one of the above mentioned SB's during exposure	No	SB available group: Not required SB utilization group: Required	Investigator initiated	Maintained	Yes	BAT-Subjective, Questionnaire	Baseline, Posttreatment
Telch et al., 2004	6, 5-minute trials in a claustrophobia chamber	Low cognitive load: listened to 15 neutral words that were presented repeatedly (e.g., "banana") High cognitive load: participants listened to different tones and indicated if they were the same or different	Yes	Required	Investigator initiated	Maintained	Yes	BAT-Physio, BAT-Subjective	Baseline, Posttreatment

Table 6, cont.

Author(s) & Publication Year	Exposure Description	Safety Behavior Description	Distra-ction Study	Required vs. Not Required	Naturally Occurring vs. Investigator Initiated	Safety Behaviors Maintained vs. Faded Across Treatment	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
van den Hout et al., 2001	Writing "I hope [name of friend or relative] is in a car accident" followed by closing eyes and thinking about the situation for a few seconds (tailored slightly if participants refused, or if they did not reach at least SUDS of 50 on the test)	Participants were told that they may do whatever they wish to try to reduce or cancel the effects of writing the sentence (e.g., tearing the sheet with the written-out sentence).	No	Required	Either	Maintained	No	BAT-Subjective	Baseline, End treatment
van den Hout et al., 2002	Exposure to uncomfortable Thought-action-fusion sentence. "I hope…. is in a car accident." Then imagine the situation. Made sure it produced a SUDs rating of 50 or above, if not, visualization were made more intense.	Participants were told that they may do whatever they wish to try to reduce or cancel the effects of writing the sentence (e.g., tearing the sheet with the written-out sentence).	No	Required	Either	Maintained	Both	BAT-Subjective	Baseline, End treatment, Posttreatment
van den Hout et al., 2011	Touching one item (picked from 6 baseline items) rated as most contaminated. 20 times per session with a 30 second break between trials. 2 sessions about, 2 weeks apart	Using as many disinfectant wipes as desired for up to 30 seconds between each trial.	No	Required	Investigator initiated	Maintained	Yes	BAT-Subjective	Baseline, Posttreatment
van den Hout et al., 2012	20 trials of touching a contaminant (1 out of 6 rated as highest contamination rating at baseline)	Use of liquid disinfectant between trials	No	Required	Investigator initiated	Maintained	Both	BAT-Subjective	Baseline, End treatment, Posttreatment

Table 7: Description of relevant design features for safety behaviors removed studies.

Author (s) & Publication Year	Exposure Description	SB Description	Distraction Study	SB Methodological Taxonomy	Assessments Under Equivalent Conditions	Outcome Assessment Type	Assessment Time Points
Kim, 2005	5-minute speech presentation on "friendship in college students" that was videotaped. Subjects were told they would be rated by 10 undergrads on ideas and attitude presented	Provided instructions to not use idiosyncratically identified safety behaviors	No	Naturally occurring	No	BAT-Subjective	Baseline, End treatment
Morgan & Raffle, 1999	10 days (80 hr) of treatment and 1 week of unsupervised exposure - social phobia group treatment	Instructions to drop safety behaviors used by patient in social situation	No	Naturally occurring	Yes	BAT-Subjective, Questionnaire	Baseline, Posttreatment
Salkovskis et al., 2006*	Rationale followed by two 1.5 hour sessions of exposure. Exposure procedure was idiosyncratic to the individual's agoraphobic complaints	Idiosyncratic to the individual	No	Naturally occurring	Yes	BAT-Subjective, BAT-Approach, Questionnaire	Baseline, Posttreatment
Taylor & Alden, 2010 (Study 1)	5-minute discussion with a confederate. Open-ended "getting to know you" conversation.	Idiosyncratic (identified using an interview)	No	Naturally occurring	No	BAT-Subjective, BAT-Approach	Baseline, End treatment
Taylor & Alden, 2010 (Study 2); Taylor & Alden, 2011	5-minute discussion with a confederate. Open-ended "getting to know you" conversation.	Idiosyncratic (identified using an interview)	No	Naturally occurring	No	BAT-Subjective, BAT-Approach	Baseline, End treatment

Note. *Salkovskis et al., 2006 used the same sample as Salkovskis et al., 1999. To avoid data dependency due to the shared sample, data were used from the final endpoint in Salkovskis et al., 2006.

ADDING SAFETY BEHAVIORS TO EXPOSURE THERAPY (SB+): PRELIMINARY ANALYSES

Equivalent Versus Non-Equivalent Testing Conditions

We began analyses by investigating the impact of assessing outcome when treatment groups were and were not equated for the availability or use of safety behaviors. Among the studies focused on the addition of safety behaviors (SB+), results suggest that the equivalence of testing conditions had a statistically significant influence on effect size ($Q(1) = 4.10$, p = .04). The addition of safety behaviors produced a trend for lower symptom levels when testing conditions were non-equivalent ($g = -0.15$; $p = .08$); and the addition of safety behaviors produced no statistically significant impact on symptom level when the testing conditions were equivalent ($g = 0.05$; $p = .30$; see Table 8). Due to the moderating effect of the equivalence of testing conditions, and the methodological problems associated with using non-equivalent testing conditions to compare treatment groups, we performed the remaining analyses solely using the effect sizes that represented equivalent testing conditions.

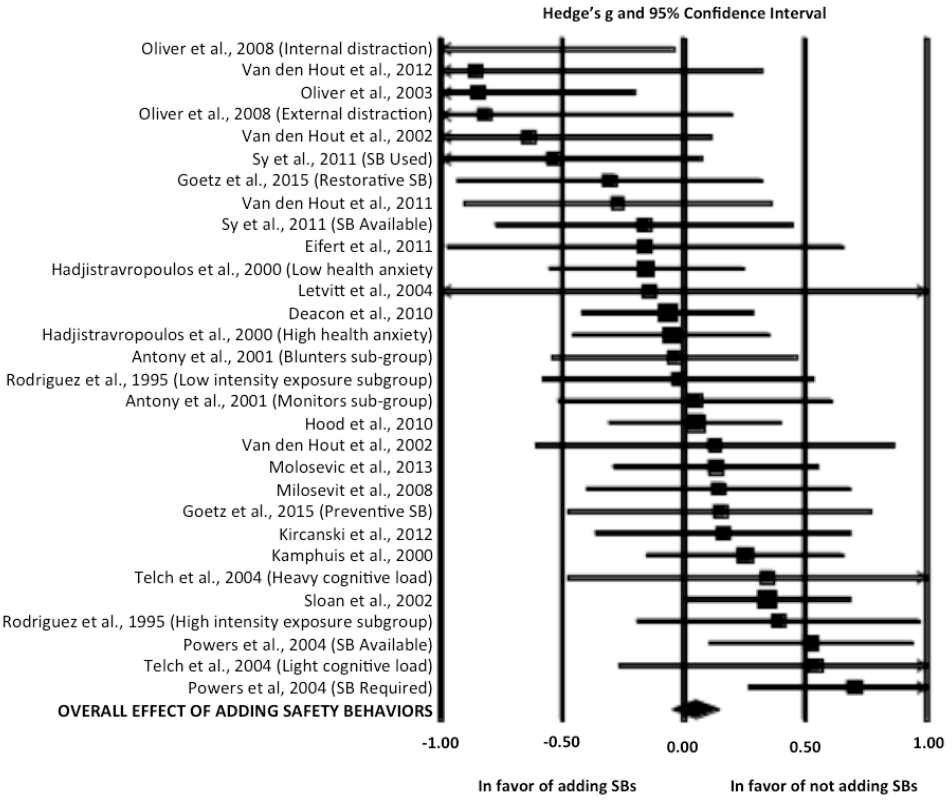
Heterogeneity

After effect sizes for non-equivalent testing conditions were removed, 30 unique between-group comparisons remained in the sample of studies. To justify testing additional moderator testing, we evaluated the heterogeneity of remaining effect sizes. Heterogeneity was greater than what would be expected by sampling error alone ($Q(29) = 50.01$, $p = .01$). This justified further testing of moderators to explore potential contributors to the heterogeneity in effect sizes.

ADDING SAFETY BEHAVIORS TO EXPOSURE THERAPY (SB+): PRIMARY OUTCOME

Of the 30 studies that assessed the impact of adding safety behaviors to exposure therapy, 14 effect sizes were in a positive direction, and 16 were in a negative direction (see Figure 3). The effect sizes for each study ranged from -1.10 to 0.71. The weighted average effect size (*g*) in the fixed effects model was estimated as 0.05 with a 95% confidence interval from -0.05 to 0.15, suggesting that overall, the addition of safety behaviors during exposure therapy did not impact treatment outcome. The random effects model produced similar results (*g* = .01; 95% CI = -0.12 to 0.15; p = .84).

Figure 3: Forest plot for effect sizes of studies comparing exposure therapy with safety behaviors added to an exposure therapy control group.



Note. SB = safety behaviors.

ADDING SAFETY BEHAVIORS TO EXPOSURE THERAPY (SB+): MODERATOR TESTS

Assessment-Related Moderators

We tested whether the modality of assessment impacted effect size across four different types of assessments: (1) avoidance behavior, (2) subjective ratings, and (3) physiological responding during a behavioral avoidance tests (BATs), and (4) responses on symptom questionnaires. Moderator testing suggested that the type of measurement did not impact effect size overall ($Q(3) = 2.07$, $p = .56$). The overall effect sizes within each modality of assessment were not different from zero (p's ≥ .11).

We then examined whether the time-point at which the assessment was conducted explained variance in effect sizes. Sample size limitations prevented us from evaluating assessment time-point in a continuous fashion using meta-regression (with only $k = 11$ follow-up effects available for analysis). Effect sizes were therefore categorized into those conducted on the same day as treatment ended (end of treatment), and those conducted one or more days after treatment was ended (follow-up). Moderator analyses suggested that measurement time-point did not impact the strength of the effect size ($Q(1) = 1.17$, $p = .28$), and the Hedge's g estimate for the effect size at each of the two time points was not different than zero (p's ≥ .15).

Moderating Study Characteristics

Studies were grouped into categories based on the clinical severity of the recruited population (studies that had no inclusion criteria for clinical severity/used a general sample, those that recruited a symptomatic population, and those that recruited a population meeting diagnostic criteria for the condition targeted during exposure-based treatment). These categories did not moderate effect size ($Q(2) = 1.65$, $p = .44$), and Hedge's g point estimates were no different from zero for each of the three categories (p's ≥ .16).

Studies were next grouped by the diagnostic condition corresponding to the symptoms targeted by the treatment. The most common treatment target was specific phobia symptoms. Studies were therefore categorized into whether they involved exposure therapy targeting specific phobia symptoms versus exposure therapy targeting symptoms associated with other diagnostic conditions. Moderator analysis suggested a significant impact of this distinction ($Q(1) = 5.94$, p = .01), such that exposure therapy targeting specific phobia symptoms was less effective when safety behaviors were added (g = .12; 95% CI = .01 to .23; p = .03), and exposure therapy targeting other psychological conditions was not impacted by adding safety behaviors (g = -.16, 95% CI = -.35 to .04, p = .11).

Moderating Safety Behavior Characteristics

The next three moderation tests involved studying variables related to the safety behaviors themselves. The effect sizes for studies manipulating distraction were not statistically different from those manipulating other types of safety behaviors ($Q(1)$ = 1.13, p = .29). Furthermore, the effect size estimates within each of these two groups did not differ from zero (p's ≥ .14).

Studies were furthermore categorized into those in which the instruction set in the safety behaviors added group required the performance of safety behaviors versus those in which safety behaviors were available but not required to be used. The moderator test yielded a marginal effect ($Q(1) = 3.05$, p = .08), such that adding and then requiring the use of safety behaviors did not have a statistically significant impact on symptom outcomes (p = .99), but making safety behaviors available without requiring their use led to higher symptom levels at the end of treatment (g = .20; 95% CI = .01 to .38; p = .04).

Finally, studies were categorized into those that involved the addition of safety behaviors that were selected by the investigator ("investigator initiated") as compared

with the addition of safety behaviors that were suggested by the participant ("naturally occurring"). The type of safety behavior added did not have a statistically significant impact on treatment outcome ($Q(1) = .46$, $p = .50$), and neither the effect size estimate for investigator initiated safety behaviors nor for naturally occurring safety behaviors was different from zero (p's ≥ .23).

Table 8: Moderator tests for studies testing the addition of safety behaviors to exposure therapy.

Assessment Characteristics					
Outcome/Moderator	*k*	*g*	95% confidence interval		Q_b
			Low Estimate	High Estimate	
Testing Equivalence					4.10*
Equivalent	30	0.05	-0.05	0.15	
Non-equivalent	12	-0.15†	-0.32	0.02	
Type of measurement					2.07
BAT- Approach	11	-0.05	-0.38	0.28	
BAT- Subjective	24	0.13	-0.03	0.29	
BAT- Physiological	9	0.11	-0.18	0.39	
Questionnaire	17	-0.01	-0.16	0.14	
Time Point					1.17
End of treatment	30	0.02	-0.09	0.13	
Follow up	11	0.15	-0.05	0.34	

Table 8, cont.

Sample and Treatment Target Characteristics					
Outcome/Moderator	*k*	*g*	95% confidence interval Low Estimate	High Estimate	Q_b
Clinical Status					1.65
General sample	4	-0.15	-0.49	0.19	
Symptomatic	23	0.08	-0.03	0.18	
Diagnosed	3	-0.01	-0.37	0.35	
Treatment Target					5.94*
Specific Phobia	20	0.12*	0.01	0.23	
Other Diagnoses	10	-0.16	-0.35	0.04	

Safety Behavior Characteristics					
Outcome/Moderator	*k*	*d*	95% confidence interval Low Estimate	High Estimate	Q_b
Distraction Only					1.13
Distraction-Only SBs	13	-0.01	-0.17	0.14	
Not Distraction-Only SBs	17	0.09	-0.03	0.22	
SB Instructions					3.05†
SB Required	25	0.0006	-0.11	0.11	
SB Not Required	5	0.20*	0.01	0.38	
SB Selection					0.46
Investigator Initiated	27	0.06	-0.04	0.17	
Naturally Occurring	3	-0.04	-0.34	0.25	

Note. *p ≤ .05 †p ≤ .10. SB = Safety behaviors.

REMOVING SAFETY BEHAVIORS FROM EXPOSURE THERAPY: PRELIMINARY ANALYSES

Equivalent Versus Non-equivalent Testing Conditions

We first examined whether the effect sizes for removing safety behaviors from exposure therapy were dependent on whether or not the testing conditions were equivalent for safety behavior use instructions. Analyses suggested that within the SB- studies, this did not moderate effect sizes ($Q(1) = .77$, p = .38). The effect size estimates of both equivalent and non-equivalent measures suggested the benefit of removing safety behaviors (for equivalent assessments ($k = 2$); $g = .59$, 95% CI = .18 – 1.01, $p < .01$; for non-equivalent assessments ($k = 3$); $g = .37$, 95% CI = .10 – .65, $p = .01$). Due to the limited sample size, and also the fact that the equivalence of testing conditions did not moderate outcomes, we did not exclude effect sizes reflecting non-equivalent testing conditions in the remaining analyses.

Heterogeneity

Effect sizes across the five SB- studies were not significantly heterogeneous ($Q(4) = 2.90$, $p = .57$). This lack of heterogeneity could be in part due to low sample size, however, I^2, which is less dependent on sample size (Higgin, Thompson, Deeks, & Altman, 2003), similarly yielded a very low estimated of heterogeneity of effect sizes ($I^2 < .01$). Due to the lack of heterogeneity among effect sizes, further moderator testing was not indicated. Any variance in the average effect sized among these studies is likely accounted for by sampling error.

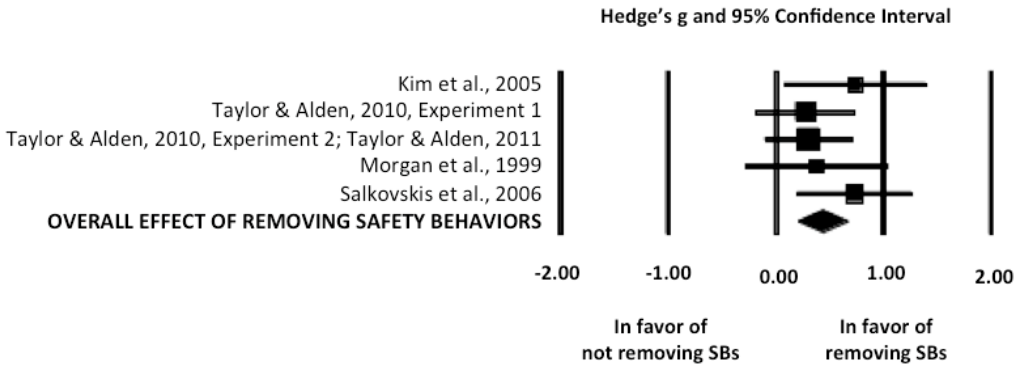
REMOVING SAFETY BEHAVIORS FROM EXPOSURE THERAPY: PRIMARY OUTCOME

Primary Outcome

All of the five studies that assessed the impact of adding safety behaviors to exposure therapy yielded an average effect in the positive direction. (see Figure 4). For individual studies, the estimated effect sizes (g) ranged from 0.28 to 0.74 (small to large

effects). In the fixed effects model, the weighted average effect size (*g*) was 0.44 with a 95% confidence interval from 0.21 to 0.67.[4] The direction of findings suggests that there were higher symptoms levels after exposure therapy that did not remove safety behaviors during therapy. In other words, data suggest that removing safety behaviors during exposure therapy yields better outcomes.

Figure 4: Forest plot for effect sizes of studies comparing exposure therapy with safety behaviors removed to an exposure therapy control group.



Publication Bias

Publication bias was investigated in the final sample of effect sizes used in the primary analyses, examining the influence of adding (SB+) and removing (SB-) safety behaviors, as compared with an exposure therapy control group. A visual examination of the funnel plot for SB+ studies suggests that there was a bias toward publishing studies showing superior outcomes for adding safety behaviors among studies with higher standard error. This is consistent with a file drawer effect, suggesting that the overall effects for the SB+ studies might be somewhat biased in favor of adding safety behaviors (see Figure 5). No publication bias was evident in the SB- studies, however, a clear visual

[4] A random effects model was also calculated, and produced effects identical to the fixed effects model, likely due to the low sample size of studies included ($k = 5$).

examination of publication bias within the sample is challenging due to the low number of studies (see Figure 6).

Figure 5: Funnel plot for studies testing exposure therapy with and without the addition of safety behaviors.

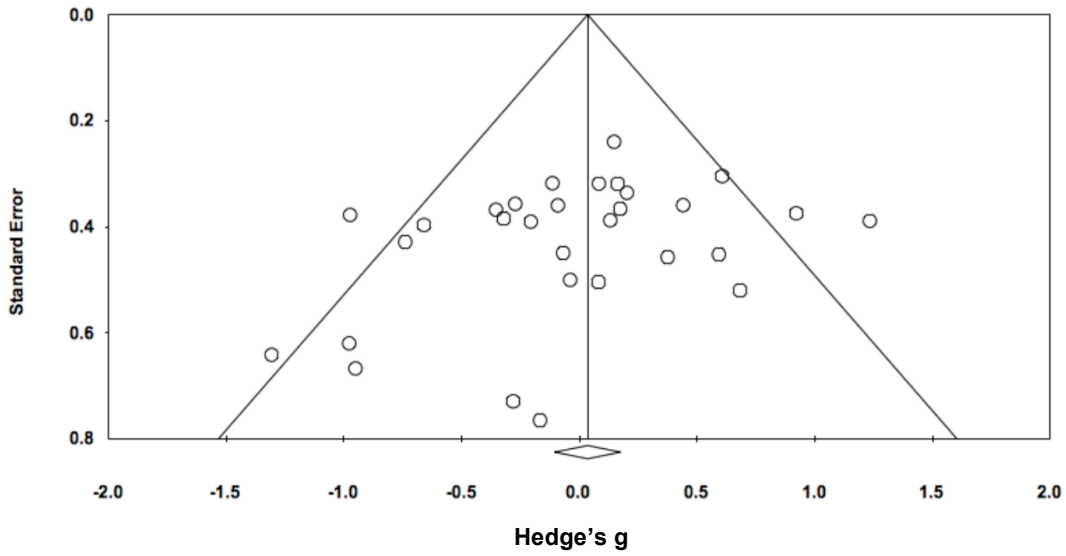
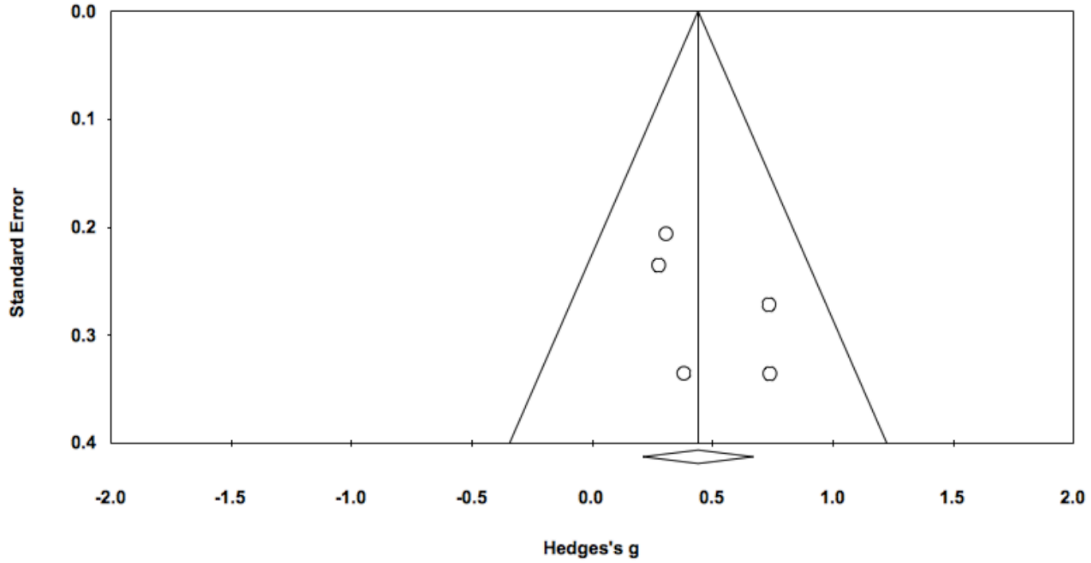


Figure 6: Funnel plot for studies testing exposure therapy with and without the removal of safety behaviors.



Discussion

We conducted a meta-analysis to evaluate the overall impact of adding (SB+) and removing (SB-) safety behaviors from exposure therapy. Findings suggest that adding safety behaviors to exposure therapy produced no overall effect on treatment outcome. However, a closer look at the data reveals significant heterogeneity among effect sizes, which was explained by a few moderators. First, the equivalence of testing conditions in their safety behavior use/availability was found to moderate effect sizes. Comparisons with non-equivalent testing conditions (in which one group had access to safety behaviors and the other did not), artificially inflated the benefits of adding safety behaviors to exposure therapy. After removing assessments with non-equivalent testing conditions, we found that adding safety behaviors made exposure therapy less effective under certain conditions, specifically when exposure therapy targeted specific phobia symptoms (relative to other conditions), and when safety behaviors were available, but their use was not required (relative to when safety behaviors were added and their use was required).

It is possible that effect sizes were more potent among SB+ studies targeting specific phobia, relative to other psychological conditions, due to the circumscribed nature of specific phobias. The vast majority of SB+ studies involved requiring participants to use one or more safety behaviors (SBs) suggested by the investigators (investigator initiated SBs; $k = 27$) rather than allowing participants to select their own safety behaviors (naturally occurring SBs; $k = 3$). Since specific phobias involve more circumscribed fears, it is likely that investigators were better able to guess the appropriate safety behaviors to circumvent the participant's fear and increase a sense of safety. Based on this logic, one would expect that adding naturally occurring safety behaviors would be more detrimental to treatment outcome than adding investigator initiated safety

behaviors. Although in our moderator analyses we found no differences in effect size based on this variable, our test was severely limited in statistical power due to the low number of studies that have examined the addition of naturally occurring safety behaviors.

A second potential explanation for detrimental effect of adding SBs found among specific phobia studies may relate to the short treatment duration of specific phobia relative to other psychological conditions. The duration of exposure therapy within the SB+ studies was commonly quite low (typically less than an hour; see Table 6). Whereas specific phobia can be successfully treated within a single, two-hour session (Őst, 1989), treatment for other conditions such as panic disorder, social anxiety, and OCD, typically involves multiple treatment sessions (e.g., Craske & Barlow, 2007; Foa, Yadin, & Lichner, 2012; Heimberg & Becker, 2002). Since the experimental designs of these studies approximated the duration of standard specific phobia treatment more closely, perhaps the impact of adding safety behaviors to treatment was stronger, whereas to observe the impact of adding safety behaviors on exposure therapy for conditions such as social anxiety disorder, one may need a longer treatment protocol.

We were surprised to find that adding safety behaviors to exposure therapy was more detrimental to treatment outcomes when their use was not required, relative to when their use was required. Given prior research showing no differences between these two groups (Powers et al., 2004; Sy et al., 2011), we did not expect the impact to differ in our meta-analysis. However, the moderator test reached trend-level, and the point estimate (*g*) suggested a statistically significant drawback of adding safety behaviors without requiring their use. Although a tentative explanation, it is possible that internal versus external attribution of safety behavior use plays a role in this effect. Perhaps participants attribute the use of the safety behavior to their own inability to cope (internal attribution)

when its use is not required. This could have a more negative impact on treatment outcomes, relative to using safety behaviors because the experimenter requires it (external attribution). Internal attribution of safety behavior use may lead to more marked reductions in self-efficacy to cope as compared with external attribution of safety behaviors use (Bandura & Adams, 1977). However, this is a tentative hypothesis that would require further empirical examination. It is also important to interpret this effect with caution, given the trend-level of the moderator test.

Among studies that evaluated the removal of safety behaviors (SB-), we found a clear benefit for removing safety behaviors during exposure therapy, as compared with an exposure-only control condition. There was no difference among effect sizes that reflected equivalent and non-equivalent testing conditions (in terms of safety behavior instructions) within the SB- studies. Non-equivalent testing conditions within these studies would involve a comparison in which one group was still operating under instructions to remove safety behaviors, whereas the control group would have no instructions related to safety behaviors. Under both equivalent and non-equivalent testing conditions, results suggested the benefit of removing safety behaviors. Therefore, the overall effect size did not appear to be influenced by artificially dampening the impact of the SB removed group, which was tested under more challenging exposure therapy conditions when instructions for safety behavior use were non-equivalent. Furthermore, the overall effect sizes demonstrated very little heterogeneity outside what one would expect due to sampling error, which strengthens confidence in the conclusion that removing safety behaviors produces overall superior treatment outcomes.

Results from the present study aligned with a previous meta-analysis (Meulders et al., 2016) in that we found that adding safety behaviors did not impact exposure therapy outcomes on average across all studies. However, due to the heterogeneity observed

among effect sizes (another finding in common with Meulders et al., 2016), we tested various effect size moderators and were able to identify conditions under which adding safety behaviors worsened treatment outcomes. Regarding our analysis of SB- studies, findings differed somewhat from those of Meulders and colleagues (2016), who found a "borderline significant overall effect size in favor of omitting [safety-seeking behaviors]" (p. 151). The present analysis identified a clear benefit for the removal of safety behaviors.

There are several potential explanations for the discrepancy between the results in the present meta-analysis, and the results of Meulders and colleagues (2016). First, we added several study exclusion criteria to increase the methodological rigor of the studies used in our meta-analysis. For example, we removed studies that used within-subjects, crossover designs due to the potential for carryover effects. We furthermore added another study exclusion criteria not used in previous research; not only did both treatment groups have to receive exposure therapy, but exposure therapy procedures also had to be equivalent with the exception of the safety behavior manipulation (or related instructional sets). These additional exclusion criteria, while clearly coming with the drawback of lowering our sample size, might have increased our ability to detect the true impact of removing safety behaviors from exposure therapy.

It is also possible our findings differed from Meulders and colleagues (2016) because we used different procedures for coding and calculation study effect sizes. We coded multiple outcome assessments within studies, as opposed to selecting one time point and assessment (i.e., self-reported fear at the last available time point; Meulders et al., 2016). Furthermore, when pre-treatment data were available, we adjusted post-treatment outcomes for pre-treatment differences. Therefore in addition to screening out studies with more methodological problems, we also made an effort to calculate effect

sizes using procedures that would be more sensitive to detecting the true effect of the experimental manipulation.

Implications for Theoretical Development

In terms of the theoretical development, a close comparison of the actual treatment recommendations from authors on both sides of the safety behavior debate reveals that they agree more than they disagree. Authors on one side of the debate suggest that clinicians "eliminate…safety behavior as soon as possible" (Blakey & Abramowitz, 2016, p. 13) or "eliminate any safety-seeking behaviors which may be maintaining catastrophic cognitions" (Salkovskis et al., 1996); whereas authors on the other side of the debate suggest that, safety behaviors "should be used in a limited manner and only for a limited period, especially in the early stages of treatment" (Rachman et al., 2008, p. 171). Both perspectives acknowledge the importance of reducing safety behaviors over the course of exposure therapy, which has been further confirmed by our quantitative synthesis of data demonstrating the benefits of removing safety behaviors during exposure therapy.

However, only one theoretical perspective (judicious use/response induction) would predict that introducing safety behaviors could produce superior treatment outcomes, and only under the condition that safety behaviors are faded out over the course of treatment (e.g., Rachman et al., 2008). Unfortunately, even after a comprehensive review of the literature, we still cannot address the question of whether or not judiciously adding safety behaviors to exposure therapy improves outcomes. Only two out of the twenty-six identified SB+ studies evaluated the impact of adding, and then fading, safety behaviors (see Table 6). Much additional research is needed in this area before we can draw any firm conclusions on the relative benefits or drawbacks of judicious safety behavior use.

Several SB+ studies examined the use of safety behaviors that are introduced and maintained throughout treatment. However, there are no theoretical perspectives, to our knowledge, that would predict superior treatment outcomes when safety behaviors are added, and then maintained, for the full course of treatment. Our overall null findings on the impact of adding safety behaviors to exposure therapy could then be viewed as somewhat surprising (note that the vast majority of studies included in this analysis maintained safety behaviors throughout treatment). However, examination of study effect sizes reveals a high degree of variance, greater than what one would expect from sampling error alone.

This high variance in study effect sizes highlights the importance of moving away from the question of whether or not safety behaviors impact treatment outcome, and instead working towards identifying under which conditions adding safety behaviors impacts exposure therapy outcomes. In this investigation, we identified a few of these moderators (e.g., worse outcomes were found when safety behaviors were added during exposure therapy for specific phobia symptoms), but there are certainly many more moderators that could be investigated moving forward. For example, only three SB+ studies evaluated the impact of adding naturally occurring as opposed to investigator initiated safety behaviors. Further examination of the impact of adding naturally occurring safety behaviors to exposure therapy is an example of one area of research that will require additional data collection, particularly since this type of manipulation is more applicable to clinical settings. Additionally, determining whether the influence of safety behaviors is moderated by whether or not safety behaviors are faded over the course of treatment would help move forward the debate regarding the hypothesized benefits of judicious safety behavior use.

LIMITATIONS OF EXISTING RESEARCH AND FUTURE RESEARCH DIRECTIONS

Results from the present study highlight a number of limitations in the existing research on safety behaviors, which provide key directions for future research. For example, our findings highlight the importance of taking more care in the design of future studies testing the addition of safety behaviors to exposure therapy (SB+ studies). Specifically, our findings demonstrated that among SB+ studies, effect sizes were moderated by whether or not testing conditions were equivalent. Several studies evaluated differences between groups while one group had access to safety behaviors and the other did not. Our data suggest that this has the effect of falsely inflating the benefits of adding safety behaviors to exposure therapy. This methodological issue could easily be guarded against in future studies by providing a post-treatment assessment during which neither group has access to safety behaviors.

There are several additional limitations in the prior research on safety behavior use during exposure therapy, which suggest important areas for future research. Although clinical investigators are typically most interested in the end goal of translating findings to benefit treatment-seeking populations, very few studies recruited samples that met diagnostic criteria for the psychological condition under investigation (less than 25% of the studies reviewed; see Table 5). Recruitment of samples exhibiting more severe symptoms might be particularly important for further investigation of the judicious use of safety behaviors. Specifically, in his review, Rachman et al. (2008) suggested that "safety behavior ...[may be] significantly more effective than conventional therapy in treatment patients with high-intensity/severe fears" (p. 170). Given the emphasis on the idea that judicious safety behavior use might make therapy "more acceptable to patients" (Rachman et al., 2008; p.170), it will be especially important to conduct future investigations in populations with more severe fears to fully test this hypothesis.

Furthermore, given the potency of exposure therapy, it is relatively easy to reach a floor effect when treating populations with low symptom levels, which would mask the ability to detect potential influences of safety behavior use on treatment outcome. Using treatment-seeking populations in future studies would therefore provide data that would better generalize to applied clinical work.

As observed by authors of prior research reviews in this area (Helbig-Lang & Petermann, 2010), the conclusions we can draw from these studies rely entirely on the integrity of the experimental safety behavior manipulation within each study. However, manipulation checks within some safety behavior studies (e.g., Morgan & Raffle, 1999) have revealed low integrity of the manipulation, that is, ensuring that participants follow instructions to either use or suppress safety behaviors. When manipulation checks do not confirm the integrity of the safety behavior manipulation, the conclusions we can draw from study findings are severely limited. To ensure higher integrity of the manipulation of safety behaviors, it may be helpful to provide participants with repeated reminders of the instructions on safety behavior use or fading throughout exposure therapy. Participants encountering feared stimuli during exposure therapy may have difficulty attending to and following the experimental instructions they received prior to starting treatment.

In future studies evaluating the influence of adding safety behaviors, it may also be useful to allow participants to select their own safety behaviors. This is more in line with clinical practice, in which therapists would typically tailor treatment to the individual. Furthermore, this would help to eliminate the guesswork involved in investigators suggesting safety behaviors that may or may not increase a given participant's sense of safety during exposure therapy. As suggested by prior reviews (Helbig-Lang & Petermann, 2010; Telch & Lancaster, 2012), a functional evaluation of

the behavior is recommended as a prerequisite to concluding that a given behavior serves a protective function for that individual. For example, although distraction is often viewed as a safety behavior (an unnecessary protective action to reduce exposure to internal psychological distress or to reduce awareness of the feared stimulus) distraction can also serve the opposite function. For example, visual distraction from the feared stimulus (e.g., a spider) might increase the potency of exposure among patients who use hyper-vigilant attendance to a feared stimulus as a safety behavior (e.g., closely watching a spider's movement). Therefore, in future investigations, it may be useful to focus primarily on the manipulation of naturally occurring safety behaviors, or safety behaviors identified by the individual participant as (unnecessary) protective actions. Doing so would further increase the integrity of the experimental manipulation.

Another limitation the present study relates to the fact that findings may not necessarily generalize to the impact of using of safety behaviors in daily life, outside the context of formal exposure therapy procedures. Experimental studies evaluating the impact of adding safety behaviors during daily life routines provide important information of the role of safety behaviors in provoking anxiety. There have been few such studies conducted to date (Deacon & Maack, 2008; Olatunji et al., 2011); although findings thus far suggest that introducing safety behaviors in daily life increases psychopathology. Findings from the reviewed studies additionally cannot comment on the impact of fading safety behaviors, outside the context of formal exposure therapy procedures. However, findings to date on a treatment protocol focused purely on safety behavior fading highlights the promise of this intervention strategy (Schmidt et al., 2012).

Furthermore, it would be beneficial for more studies to evaluate the impact of safety behavior use (or removal) on treatment outcomes for conditions other than anxiety-related disorders. Although prior studies have identified an association between safety

behavior use and symptoms of conditions other than anxiety, such as eating disorders (Shafran, Fairburn, Robinson, & Lask, 2004), insomnia (Ree & Harvey, 2004), and chronic pain (Tang et al., 2007), there are relatively few experimental investigations of the impact of safety behavior use in disorders outside anxiety-related conditions (for an example, see Hadjistravropoulos, Hadjistravropoulos, & Quine, 2000). Although correlational studies are an excellent start, further experimental investigations are required for stronger causal inferences.

Finally, the present study was somewhat limited in terms of the number of final studies included in the analyses, particularly for the SB- studies. The relatively low sample size was in large part due to our rigorous exclusion criteria, which emphasized screening out studies with methodological weaknesses. This involved excluding studies that altered aspects of exposure therapy procedures in addition to the safety behavior manipulation, and studies that used crossover designs to investigate this learning-based paradigm. A relative strength in this screening approach, however, is that the data we evaluated produce outcomes that are easier to interpret and eliminate extraneous sources of error. This might have increased our sensitivity to detect the true effect of the safety behavior manipulation.

CONCLUSIONS

Findings from this meta-analysis highlight the clear benefits of removing safety behaviors during exposure therapy, relative to a standard exposure therapy procedure. Across studies examining the addition of safety behaviors to standard exposure therapy, we did not find an overall impact of adding safety behaviors on treatment outcomes. However, there was a high degree of variability in the study effect sizes. This highlights the importance of investigating the conditions under which adding safety behaviors during exposure therapy influences treatment outcomes. Exploratory moderator analyses

suggest that adding safety behaviors produces worse outcomes when exposure therapy targeted specific phobia symptoms (relative to other conditions), and when the use of safety behaviors was not required (relative to when their use was required). Further research is needed to address important questions in the area of safety behavior use during exposure therapy, specifically testing whether the judicious use of safety behaviors, introduced early in treatment and faded over the course of treatment, produce superior outcomes relative to exposure therapy alone.

STUDY 3 - AUGMENTING EXPOSURE THERAPY WITH PRE-EXTINCTION FEAR MEMORY REACTIVATION AND DEEPENED EXTINCTION

Approximately 28.8% of the American population will meet criteria for an anxiety disorder at some point in their lifetime (Kessler et al., 2005). Exposure therapy, either alone or in the context of cognitive-behavioral therapy, is one of the most effective treatment techniques available for anxiety disorders (Butler, Chapman, Forman, & Beck, 2006; Hofmann & Smits, 2008; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010; Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008). However, some patients do not fully respond to treatment, and other patients relapse after successful treatment (e.g., Fava et al., 2001; Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000; Foa et al., 2005), so there is clearly much room for the improvement of exposure therapy outcomes.

Decades of research have focused on the investigation of both pharmacological and non-pharmacological strategies to boost the efficacy of exposure therapy. Promising non-pharmacological techniques include strategies such as providing physiological feedback demonstrating fear reduction (Telch, Valentiner, Ilai, Petruzzi, & Hehmsoth, 2000), increasing focus on threat-disconfirming evidence (Kamphuis & Telch, 2000; Sloan & Telch, 2002), fading safety behaviors (Helbig-Lang & Petermann, 2010), and increasing the variety of feared stimuli used during exposure therapy (Rowe & Craske, 1998). Pharmacological augmentations, such as D-Cycloserine (DCS; B. M. Graham, Langton, & Richardson, 2010) and Methylene Blue (Telch et al., 2014), have also shown some evidence of boosting the efficacy of exposure therapy. These pharmacological interventions were originally developed in non-human animal research, allowing for fine-tuned testing of their neural mechanisms due to the ability to investigate molecular markers of neural change in a variety of brain regions after euthanizing animals.

Although DCS and Methylene Blue were translated from the animal literature on fear extinction (Bouton, Vurbic, & Woods, 2008; Gonzalez-Lima & Bruchey, 2004), there has been surprisingly little research translating non-pharmacological exposure augmentation strategies recently developed in the context of animal research. This study will test the use of two of these behavioral strategies: pre-extinction fear memory reactivation and deepened extinction.

PRE-EXTINCTION FEAR MEMORY REACTIVATION (PE-FMR)

The traditional procedure for exposure therapy involves repeated or prolonged extinction trials. Extinction training (as it is called in animal models) or exposure therapy (as it is called in treatment models) involves the repeated or prolonged presentation of a fear-provoking stimulus in the absence of the feared consequence, persisting until the fear response subsides. However, researchers have found that, even when fear subsides after exposure therapy, the fear response can re-emerge under a number of conditions. For example, fear is more likely to re-emerge when the feared stimulus is encountered in an environment dissimilar to the one used during extinction training (Bouton, 1993; 2000; 2002). Researchers posit that extinction therefore creates a context specific memory that inhibits fear when activated, but leaves the original fear memory trace intact. In other words, exposure therapy produces a second inhibitory memory that competes with the original fear memory for expression. When the inhibitory memory is not activated (e.g., in environments dissimilar to extinction training), the maladaptive fear response returns (Bouton, 1993; 2000; 2002).

Alternatively, some researchers have suggested that, rather than creating a secondary competing/inhibitory memory, it might be possible to eliminate return of fear by directly "updating" the initial fear memory (Clem & Huganir, 2010; Monfils, Cowansage, Klann, & LeDoux, 2009; Nader, Schafe, & Le Doux, 2000; Schiller et al.,

2010; Xue et al., 2012). Consolidation theory asserts that new memories do not immediately consolidate (or solidify), and instead are susceptible to updating for a critical window of time prior to consolidation (Dudai, 1996). Analogously, recent research suggests that a consolidated fear memory can re-enter a labile state (i.e., "re-consolidation") when the memory is activated via a brief encounter with the feared stimulus. Specifically, data from rodent models demonstrate that fear memories that have been re-activated by a single, brief encounter with the feared stimulus are then susceptible to disruption and/or updating during the 6-hour window after reactivation (Monfils et al., 2009; Nader et al., 2000). According to the proposed reconsolidation update mechanism (Monfils et al., 2009), exposure therapy conducted within the reconsolidation window would produce more persistent fear attenuation. In other words, the new information about the safety of the feared stimulus acquired during exposure therapy is assimilated into the fear memory when it reconsolidates, directly "updating" the original fear memory trace.

In a series of basic conditioning experiments in rodents, Monfils and colleagues (2009) were the first to demonstrate that the addition of a reactivation trial before extinction protects against return of fear. The benefits of pre-extinction memory reactivation (PE-MR) have been replicated in animal models of fear extinction (Baker, McNally, & Richardson, 2013; Clem & Huganir, 2010; Flavell, Barber, & Lee, 2011; Shumake & Monfils, 2015), drug addiction (Ma, Zhang, & Yu, 2011; Millan, Milligan-Saville, & McNally, 2013; Xue et al., 2012), and appetitive responding (Flavell et al., 2011; Kredlow, Unger, & Otto, 2016). However, other experiments in animal models have failed to replicate the benefits of PE-MR (Chan, Leung, Westbrook, & McNally, 2010; Costanzi, Cannas, Saraulli, Rossi-Arnaud, & Cestari, 2011; Ishii et al., 2012; Ma et al., 2011; Millan et al., 2013). Researchers have suggested that procedural variations may

explain discrepant findings, such as the type of calculation used to measure return of fear (Chan et al., 2010), and the duration of the time lapse between conditioning and extinction (Costanzi et al., 2011; Kredlow et al., 2016) or reactivation and extinction (Kredlow et al., 2016; Ma et al., 2011).

In translating these animal models to humans, several studies have found that the addition of PE-MR to exposure therapy enhances the durability of memory updating (Chan & LaPaglia, 2013; Schiller et al., 2010; Xue et al., 2012). Moreover, these findings have generalized to a wide range of paradigms, including extinction of fear conditioned in the laboratory (Oyarzún et al., 2012; Schiller et al., 2010), extinction of response to drug cues in heroin addicts (Xue et al., 2012), and even updating of declarative memory (Chan & LaPaglia, 2013), with results lasting through 6-month (Xue et al., 2012) and 1-year follow-ups (Schiller et al., 2010). Imaging studies have demonstrated that pre-extinction fear memory reactivation (PE-FMR) decreases dependency on the prefrontal cortex (PFC) during fear extinction recall, supporting the engagement of a neural mechanism that is independent from PFC-dependent inhibitory learning (Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013). Although some experiments in human populations have failed to replicate the benefits of PE-FMR (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013; Drexler et al., 2014), meta-analysis suggests that overall, PE-FMR produces small to moderate effects for enhancing persistent attenuation of fear in human models (Kredlow et al., 2016). Importantly, however, previous research has primarily focused on the extinction of fear conditioned in the laboratory, as opposed to naturally acquired fears, such as the fears of patients with pathological anxiety.

A recent pilot study (N = 32) provided preliminary evidence of the effectiveness of PE-FMR in a population with naturally acquired (i.e., not laboratory-conditioned) fear of snakes or spiders (Telch, York, Lancaster, & Monfils, 2017). Results revealed that

relative to standard exposure procedures, the addition of a PE-FMR trial produced lower fear responding during a behavioral approach test in a new situation (a generalization test) at one-month follow-up (Telch, York & Monfils, 2010; Telch et al., 2017), . Participants in the PE-FMR group also experienced faster fear decline based on lower expected and peak fear ratings in the initial exposure therapy trials (Telch et al., 2017). In contrast, a second pilot study ($N = 32$) in a spider phobic sample found exposure therapy with and without PE-FMR to be equally efficacious (Shiban, Brütting, Pauli, & Mühlberger, 2015). Contrasting findings may be due to differences between the two treatment protocols. For example, Telch et al. (2017) tested the benefits of a one-session, in vivo exposure therapy protocol with and without an in vivo PE-FMR. In contrast, Shiban et al. (2015) used a two-session treatment protocol, randomizing participants to receive one session of virtual reality with and without a virtual reality PE-FMR, followed by one session of in vivo exposure (with the second, in vivo session being the same across both treatment groups and neither receiving PR-FMR prior to this session).

Telch and colleagues' (2017) findings were particularly unique in that they were the first to find that PE-FMR increases the speed of fear reduction during treatment. The increased efficiency of fear reduction might mimic the effects of some pharmacological enhancers, since they seem to trigger overlapping neural mechanisms of learning. For example, when D-Cycloserine, an NMDA (N-methyl-D-aspartate) receptor agonist, is used in conjunction with exposure therapy, it facilitates neuroplasticity and produces more rapid fear reduction across therapy sessions (Graham et al., 2010). The NMDA-agonizing effects of DCS also enhance consolidation of "successful" learning experiences, in that the facilitating effects of DCS are dependent upon successful within-session fear reduction (e.g., Smits et al., 2013). Prior research similarly suggests that NMDA receptor agonists also play a critical role in the reconsolidation of memory

(Milton, Lee, Butler, Gardner, & Everitt, 2008; Tronson & Taylor, 2007). A brief reactivation trial may therefore produce effects similar to D-Cycloserine, facilitating the speed of fear reduction and boosting consolidation of successful learning experiences.

Although findings from individual studies have been mixed, the data overall suggests that PE-FMR is a promising strategy for improving exposure therapy outcomes (Kredlow et al., 2016). However, outside of two pilot studies (each $N = 32$; Telch et al., 2017; Shiban et al., 2015), prior research focused on the extinction of laboratory-conditioned, rather than naturally acquired, fear. Additional research is needed to test the use of PE-FMR to improve exposure therapy outcomes in larger samples of participants with naturally acquired fear. Furthermore, preliminary findings suggest that PE-FMR may also increase the speed of fear reduction during treatment (Telch et al., 2017). However, it is unclear whether treatment could then be terminated earlier, while still retaining the benefits of PE-FMR.

DEEPENED EXTINCTION

Rescorla (2006) found promising effects for a second behavioral strategy called deepened extinction, a two-step procedure for enhancing fear reduction. In the deepened extinction procedure, two or more feared stimuli are first presented in isolation, until the fear response to each stimulus is extinguished individually (elemental extinction). Afterwards, the stimuli are presented simultaneously (compound extinction). The compound presentation causes a resurgence of the fear response, which is then re-extinguished (Reberg, 1972; Rescorla, 2006). According to Rescorla and Wagner's (1972) elemental model of associative learning, extinguishing two feared stimuli simultaneously produces a summation of the fear associations of the stimuli, resulting in a greater prediction error signal than if either stimulus were extinguished in isolation.

This increased error signal is hypothesized to be the operative mechanism governing the enhancement of fear attenuation brought about by the deepened extinction procedure.

In contrast to the idea that greater prediction error would lead to greater extinction learning, prior studies in animals and humans have found that presentation of aversive stimuli in compound can block fear extinction associated with the individual stimuli (Pineño, Zilski, & Schachtman, 2007; Vervliet, Vansteenwegen, Hermans, & Eelen, 2007). However, in these studies, the feared stimuli were not presented independently prior to compound extinction, which Rescorla (2006) suggests may be a critical element of the deepened extinction procedure. Specifically, he suggests that when two excitatory stimuli are presented in compound, they compete for associative learning. He describes that an overshadowing effect can occur when the stimuli differ in their salience, in that the more "salient" (or more feared) stimulus will take on more of the associative learning, preventing associative learning for the relatively less salient stimulus. He suggests the deepened extinction procedure will protect against overshadowing by ensuring that each stimulus is equally "salient" by the process of extinguishing their fear responses elementally prior to compound extinction.

Other researchers (Culver, Vervliet, & Craske, 2015) suggest that presentation of the stimuli individually before in compound promotes elemental processing and summation of the stimulus' excitatory properties. This ensures that the stimuli are not processed together during compound extinction as one whole and distinct stimulus configuration (see Pearce, 1987 for a competing model predicting configural processing). If the two stimuli presented together are processed as one whole configuration rather than as two elements together, this would prevent the desired fear-summation and deepened extinction effects. Thus, researchers suggest that prior learning in an elemental fashion might promote elemental processing of stimuli during compound extinction (Culver et

al., 2015; Vervliet et al., 2007). Overall, theoretical rationale and prior research are consistent with the idea that extinguishing both stimuli elementally before compound presentation is critical for promoting deepened fear extinction. In practical terms, conducting elemental prior to compound extinction is also consistent with the graduated fear extinction procedures most commonly used in evidenced-based treatments for anxiety disorders (e.g., Barlow & Craske, 2006; Foa, Hembree, & Rothbaum, 2007).

Several studies have demonstrated the efficacy of the deepened extinction procedure. In an experiment involving extinction of conditioned fear in rodents, Rescorla (2006) was the first to demonstrate that following elemental with compound extinction led to less return of fear than elemental extinction alone. This pattern of findings has been extended to the extinction of appetitive conditioning in rodents (Janak & Corbit, 2010; Rescorla, 2006), cocaine addiction in rodents (Kearns, Tunstall, & Weiss, 2012), and Pavlovian sign tracking in pigeons (Rescorla, 2006). Relatively recently, it was replicated in a fear conditioning and extinction paradigm in humans (Culver et al., 2015). Surprisingly, these promising findings have yet to be empirically tested as a method of boosting the efficacy of treatment for anxiety disorders.

PURPOSE

The primary aim of this study is to investigate the singular and combined effects of PE-FMR and deepened extinction for enhancing outcomes of exposure therapy in a large sample (N = 130) of participants with pathological fear of snakes or spiders. The primary prediction is that PE-FMR and deepened extinction will each independently enhance fear reduction relative to control groups without these augmentations, and that their combined use will produce the most potent fear reduction. Secondly, we predict that PE-FMR will produce more rapid fear reduction during exposure therapy, replicating the effects observed in a smaller pilot study (Telch et al., 2017). To build on this prior

research, we will test whether the benefits of PE-FMR are retained, even when treatment is ended earlier among participants who reach a threshold of low fear responding earlier in treatment.

Methods

PARTICIPANTS

Participants (ages 18-65) displaying a marked fear of spiders or snakes were recruited from the community and from college psychology courses. Marked fear was operationalized on the pre-screening assessment as (a) scoring 70 or higher on an online version of the Fear of Snakes/Spiders Questionnaire (Szymanski & O'Donohue, 1995), and (b) answering "no" on a yes/no question, "Would you be able to touch a spider/snake with your bare hands?" After meeting pre-screening criteria, participants then completed an in-person screening visit during which they were assessed for exclusion criteria, which included: (a) insufficient fear level, defined as ability to place hand flat on the bottom of a tank containing the feared animal, or ability to touch the feared animal with a bare fingertip in the context of behavioral approach tests; (b) concurrent treatment for fear of snakes or spiders, or (c) change in medication status during the previous month. (See Table 9 for demographic characteristics of participants.)

Table 9: Demographics of participants screened and treatment completers.

	Participants Screened N = 280		Treatment Completers N = 130	
Age				
	M = 19 Range 18-34	SD = 1.59	M = 19 Range 18-34	SD = 2.04
Target Fear Stimulus				
Spider	N = 144	51.43%	N = 87	66.92%
Snake	N = 136	48.57%	N = 43	33.08%
Gender				
Male	N = 62	22.14%	N = 26	20.00%
Female	N = 218	77.86%	N = 104	80.00%
Ethnicity				
Non-Hispanic	N = 202	72.14%	N = 88	67.69%
Hispanic	N = 78	27.86%	N = 42	32.31%
Race				
Caucasian/White	N = 185	66.07%	N = 87	66.92%
American Indian/Alaska Native	N = 6	2.14%	N = 5	3.85%
Asian	N = 68	24.29%	N = 29	22.31%
African American/black	N = 21	7.50%	N = 9	6.92%

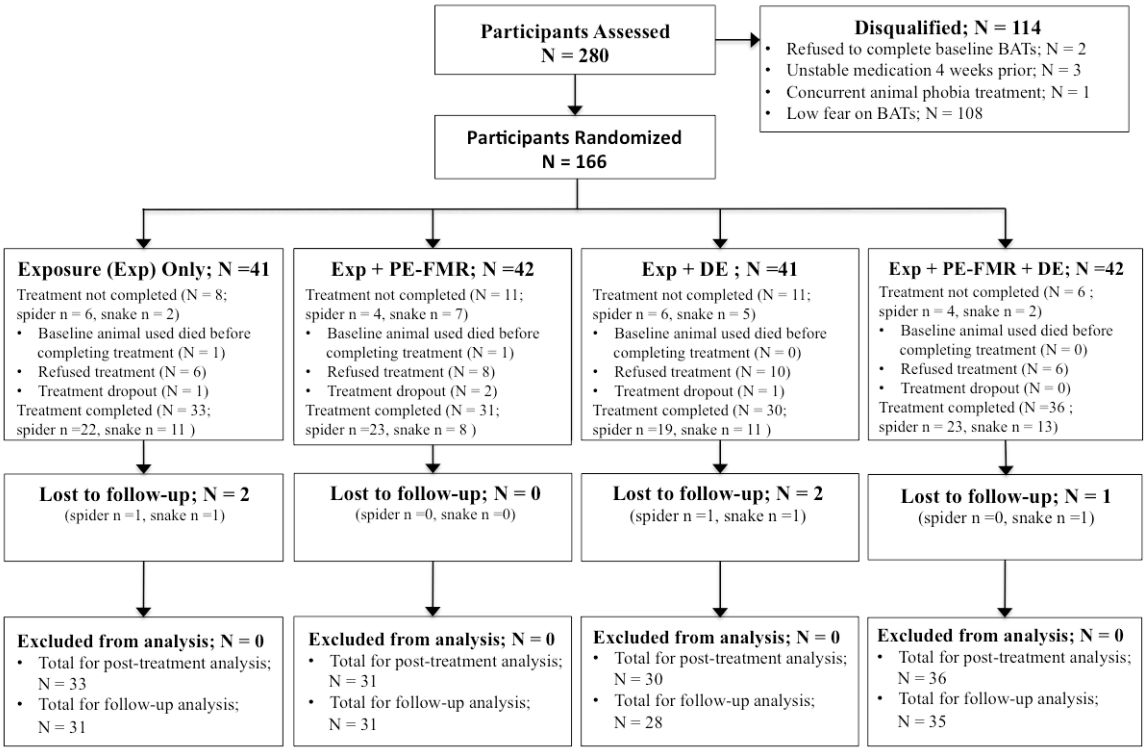
STUDY DESIGN

The first study visit served as the prescreening assessment of study exclusion criteria, and also served as a formal pretreatment assessment. During this visit, participants completed a battery of self-report rating scales and two different behavioral approach tests (see measures). Eligible participants were then stratified based on their target fear (snake or spider) and baseline severity of peak, self-reported fear during the generalization BAT[5], and randomized to one of four exposure conditions: (a) exposure therapy as usual, (b) exposure therapy with PE-FMR, (c) exposure therapy with deepened extinction (DE), and (d) exposure therapy with both PE-FMR and DE (see Figure 7). All

[5] The first 18 participants who qualified for study participation were stratified as above or below a cutoff of a peak fear rating of 75 or higher out of 100 on the generalization BAT. Most participants in this group fell into the higher fear category. Therefore, after this point, participants were stratified as above or below a cutoff of a peak fear rating of 83 (the median peak fear rating for the first 18 participants who qualified for study participation).

exposure treatment was completed in one session approximately one week after baseline assessment (*M* = 6 days, 10.28 hours; *SD* = 3 days, 0.58 hours). Two behavioral approach tests (in the treatment context and in a generalization context) were completed at baseline, immediately after treatment (post-treatment), and at follow-up approximately one week after treatment (*M* = 8 days, 7.47 hours; *SD* = 2 days, 3.82 hours). Questionnaire measures of phobia severity were completed at baseline and one-week follow-up. The Institutional Review Board at the University of Texas at Austin approved all study procedures.

Figure 7: Participant flow diagram.



Note. PE-FMR = Pre-extinction (25 minutes prior) fear memory reactivation. DE = Deepened extinction.

STUDY PROCEDURES

Figure 8 provides a visual timeline for the therapeutic procedures implemented in each treatment arm.

Figure 8: Therapeutic procedures for each treatment arm.

Treatment Assignment	Time Lapse Between Reactivation and Exposure	Exposure Phase 1 Duration = To Individualized Criterion	Exposure: Phase 2 Duration = To Individualized Criterion	Exposure: Phase 3 Duration = 12 Minutes
Exposure Only	6 days*	A	B	A
Exposure + PE-FMR	25 minutes	A	B	A
Exposure + DE	6 days*	A	B	AB
Exposure + PE-FMR + DE	25 minutes	A	B	AB

Note. A = Exposure to spider/snake 1. B = Exposure to spider/snake 2. AB = Exposure to spiders/snakes 1 and 2 simultaneously. *Average duration between baseline visit and treatment visit. PE-FMR = Pre-extinction fear memory reactivation.

TREATMENT PROCEDURES

Procedures Common to All Exposure Conditions

Exposure therapy included three phases (see Figure 8). All participants completed the same procedure for phases 1 and 2. Phase one consisted of exposure to one spider or snake (stimulus A) alone, and phase two consisted of exposure to a second spider or snake (stimulus B) alone. Participants were randomly assigned one of two potential snakes or spiders as stimulus A, and were assigned the remaining spider or snake as stimulus B. Spiders included a Chilean rose tarantula (Grammostola rosea) and an Arizona blonde tarantula (Aphonopelma chalcodes). Snakes included a common corn snake (Elaphe guttata) and a Mexican milk snake (Lampropeltis triangulum annulata).

During each treatment phase, participants worked through eight progressively challenging approach steps: (1) standing five feet away from an open tank with the feared animal inside, (2) standing three feet away from the tank, (3) standing directly in front of the tank (heels one foot away from the tank), (4) placing one hand even with the top of the tank, (5) lowering one hand to one-third of the tank's depth (total of 12 inches in depth), (6) lowering one hand to two-thirds of the tank's depth, (7) touching the bottom of the tank with the fingertips of one hand, and (8) placing the palm of one hand flat on the bottom of the tank. Participants were permitted to move from one step to the next as soon as they felt able to do so throughout treatment. Additionally, they were specifically instructed by experimenters to move to the next step when their self-reported fear reached 25 or below on a 100-point scale.

Phases 1 and 2 of exposure therapy terminated when an individualized criterion was met, when either (a) the participant demonstrated sufficient habituation by reporting a fear level of 25 or below (mild fear) on the final approach step, or (b) the participant reached a time maximum of 40 minutes. (The time limit was selected to ensure that the full treatment could be implemented within one visit.) These first two phases were terminated based on individualized criteria rather than a set duration. We selected individualized criteria because researchers have posited that it is critical to extinguish the fear response to both stimuli individually before beginning compound extinction (Rescorla, 2006). Furthermore, assuming that PE-FMR produces more rapid fear reduction, we would then be able to determine whether the benefits of PE-FMR would be retained even when treatment was ended earlier.

Pre-Extinction Fear Memory Reactivation (PE-FMR)

The fear memory reactivation procedure consisted of two, 10-second phases. During phase 1, participants called to mind the sensory details of a real or imagined

encounter with the feared animal while looking at the actual animal contained in an open, clear tank on the table. During phase 2, the participant attempted to touch the bottom of the tank containing the animal. For the reactivation procedure, we used the first animal confronted during treatment (stimulus A; see Figure 8). This two-part procedure was selected to ensure the full activation of the fear memory, including activating a fear response and engaging the most potent episodic memory available.

Participants assigned to the two PE-FMR augmentation conditions (groups 2 and 4) completed the reactivation procedure at the beginning of their second/treatment visit to the lab. After reactivation, they completed a 25-minute distraction break before exposure therapy, during which they watched a re-run of a television show, an episode of Seinfeld titled "The Chinese Restaurant." The use of distraction helped to ensure that participants' thoughts were shifted from the feared animal, providing the requisite period of disengagement from the feared stimulus after retrieval (Monfils et al., 2009). We selected a 25-minute duration of disengagement because the reconsolidation update mechanism is active between 10 minutes and 1 hour after retrieval, but is no longer active at 6 hours after retrieval (Monfils et al., 2009).

PE-FMR Control

Participants without the PE-FMR augmentation (Groups 1 and 3) completed the reactivation procedure at the end of their baseline assessment (one to fourteen days before the treatment visit; minimum = 19 hours, maximum = 14 days, 1 hour; *M* = 6 days, 10.28 hours, *SD* = 3 days, 0.58 hours). The time lapse of at least one day between retrieval and treatment ensured that exposure therapy occurred well outside the 6-hour window of time in which the reconsolidation-update mechanism is presumably activated (Monfils et al., 2009). To provide further experimental control, these participants also watched the Seinfeld episode just before treatment.

Deepened Extinction

Groups 3 and 4 received deepened extinction during phase 3 of exposure therapy (see Figure 8). The procedure for deepened extinction was identical to the procedure used during phases 1 and 2 of treatment with one stimulus, except two tanks were used, one containing stimulus A used during phase 1 of treatment, and the other containing stimulus B used during phase 2 of treatment. The tanks were placed side by side on the table. Participants proceeded through the same approach steps used during phases 1 and 2. The only difference in procedure was that for steps 4 through 8, the participants lowered each of their hands into one of the two tanks. Phase 3 was terminated after 12 minutes.

Deepened Extinction Control

Groups 1 and 2 did not receive deepened extinction. To ensure equivalent duration of exposure treatment, participants in Groups 3 and 4 completed 12 extra minutes of exposure to the feared animal used during phase 1 of treatment (Stimulus A).

ASSESSMENTS

Assessments included two behavioral approach tests and five self-report questionnaires used in previous studies for the assessment of spider or snake fear. Behavioral approach tests were completed at the baseline/screening visit, at the end of exposure treatment (visit 2), and at 1-week follow-up. Questionnaires were completed at baseline and one-week follow-up.

Treatment Process Measures

At the end of each minute during treatment, subjective fear level was assessed on a 100-point scale, with the anchors of 0, no fear at all, to 100, the highest fear level imaginable. Behavioral approach also was recorded on an 8-point Guttman scale representing the treatment step the participant was on when they reported their fear level.

Behavioral Approach Test, Treatment Context (BAT-T)

BAT-T provided a test of phobic responding in the exposure treatment context. During BAT-T, participants approached stimulus A (the first animal confronted during treatment) by working through the same eight progressively difficult approach steps used during treatment: (1) standing five feet away from an open tank with the feared animal inside, (2) standing three feet away from the tank, (3) standing directly in front of the tank, (4) placing one hand even with the top of the tank, (5) lowering one hand to one-third of the tank's depth, (6) lowering one hand to two-thirds of the tank's depth, (7) touching the bottom of the tank with the fingertips of one hand, and (8) placing the palm of one hand flat on the bottom of the tank. Participants were instructed to progress through as many of the eight steps as possible within 15 seconds. Phobic response during BAT-T was assessed in two domains: (1) subjective report, as measured by participant ratings of anticipated and peak fear and disgust on a scale ranging from 0, none at all, to 100, the highest level imaginable, and (2) behavioral approach scored using a 8-point Guttman scale corresponding to the number of steps completed (1 – 8).

Behavioral Approach Test, Generalization Context (BAT-G)

This test provided an assessment of phobic responding in a non-treatment context, thus providing an index for assessing treatment generalization. During BAT-G, participants were asked to perform up to four behavioral approach steps for five seconds each using different animals than those used during treatment – a Mexican golden red rump tarantula (Brachypelma albiceps) for spider phobic participants and a coral corn snake (Pantherophis guttatus) for snake phobic participants. The tasks included: (1) touching the animal (held by an experimenter) with a Q-tip and a gloved hand, (2) touching the animal (held by an experimenter) with one finger of a gloved hand, (3) touching the animal (held by an experimenter) with one finger of a bare hand, and (4)

holding the animal with bare hands. The task was discontinued if a participant discontinued one of the four steps before the full five-second duration was completed. BAT-G was scored using a 5-point Guttman Scale corresponding to the number of BAT-G items successfully completed (0 to 4), and subjective phobic response was assessed in the same manner as in BAT-T.

Questionnaires

Participants received questionnaires tailored toward their target fear (either snakes or spiders). Since the questionnaires selected were originally developed to assess either snake phobia or spider phobia (but not both), we created an adapted version of each questionnaire so that the same questionnaire could be used to assess both groups. Minimal adaptations were made to the questionnaires to keep them as similar as possible for the snake and spider phobic participants. For example, if a questionnaire was originally designed to assess snake phobia, the word snake was replaced with spider throughout the questionnaire. (Adapted scales are available upon request.)

Fear of Spiders/Snakes Questionnaire (FSQ)

The FSQ is a self-report questionnaire originally developed to assess fear of spiders. We created a second version of this questionnaire to assess fear of snakes as well. For this questionnaire, participants endorse their level of agreement with each of 18 spider or snake-phobic thoughts on a Likert scale from 0, strongly disagree, to 6, strongly agree. The FSQ has good internal consistency, test-retest reliability, and convergent validity (Szymanski & O'Donohue, 1995). It can successfully discriminate between phobics and nonphobics and detect change over time as a function of treatment response (Szymanski & O'Donohue, 1995). Factor analysis suggests that it assesses for two distinct dimensions of specific phobia, including a dimension related to avoidance/help seeking and a dimension related to fear of harm (Szymanski & O'Donohue, 1995). The

FSQ had good internal consistency in present study sample (N = 130 treatment completers; α = .82).

Spider/Snake Beliefs Questionnaire (SBQ)

The SBQ is a self-report questionnaire originally developed to assess fear of spiders (Arntz, Lavy, & Van den Berg, 1993). We created a second version of the questionnaire to assess fear of snakes. The scale includes 78 statements regarding phobic responses to encounters with a spider or snake. Participants rate each statement on a scale from, 0, I do not believe it at all, to 100, I absolutely believe it. Psychometric evaluation revealed good internal consistency and adequate test-retest reliability (Arntz et al., 1993). The SBQ discriminates between phobic and nonphobic individuals and has good convergent validity with other phobia assessments (Arntz et al., 1993). The SBQ had excellent internal consistency in the present study sample (α = .97).

Agoraphobic Cognitions Questionnaire for Snake/Spider Phobia (ACQ-S)

The ACQ-S is a 17-item assessment adapted by Radomsky and colleagues (1996) from the Agoraphobic Cognitions Questionnaire (ACQ; Chambless, Caputo, Bright, & Gallagher, 1984) to assess for cognitions related to snake phobia. We created a second version of the scale to assess for spider phobia. This scale includes 12 items from the ACQ that measure physical concerns and cognitions about loss of self-control and in a feared situation, and five additional items that specifically address cognitions about the feared animal. This scale has excellent internal consistency (Milosevic & Radomsky, 2008), and the scale upon which it is based (the ACQ) has adequate psychometric properties (Chambless et al., 1984). The ACQ-S had excellent internal consistency in the present study sample (α = .87).

Self-Efficacy Questionnaire for Spider and Snake Phobia. (SEQ)

The SEQ is two-part, self-report questionnaire in which participants rate their confidence (on a scale from 0 percent to 100 percent confident) that they could (a) perform the eight approach steps used during treatment (SEQ- Behavioral), and (b) cope with feelings and consequences of the anxiety produced by approaching the feared animal (SEQ-Anxiety). The SEQ–Behavioral and SEQ–Anxiety were constructed for the purpose of this study, but based on Bandura's recommendations for constructing self-efficacy scales (Bandura, 2006), and on a self-efficacy questionnaire designed and psychometrically validated for assessing claustrophobia coping self-efficacy (Valentiner, Telch, Ilai, & Hehmsoth, 1993). Both the SEQ–Behavioral and SEQ–Anxiety had excellent internal consistency in the present study sample (α = .92 for each of the two scales).

Armfield & Mattiske Disgust Questionnaire (AMDQ)

The AMDQ includes 8 self-report questions in which participants rate their disgust response from 0, strongly disagree, to 6, strongly agree. It was originally developed to assess response to potentially disgust-eliciting features and situations involving a spider, but we created a second version to assess disgust response to snakes as well. The original version of the AMDQ has demonstrated adequate internal consistency in prior research (Armfield & Mattiske, 1996). The AMDQ also had acceptable internal consistency in the present study sample (α = .78).

DATA ANALYSIS PLAN

Preliminary Analyses

Prior to outcome analyses, we evaluated differences between participants who refused treatment and participants who completed treatment. Categorical data (e.g.,

demographic categories) were evaluated with chi-squared tests of independence, continuous data (e.g., sum scores on questionnaires at baseline) were evaluated using independent samples *t*-tests, and ordinal data (e.g., highest step achieved on the BAT-T and BAT-G at baseline) were assessed using proportional ordered logistic regression.

Proportional ordered logistic regression was used as opposed to other ordinal tests (e.g., Spearman's correlation) because it can account for a high number of ties in the data. (The restricted range of the Guttman scales on the BAT-T and BAT-G ensure that several participants will tie for equivalent rankings if rank-ordered from least to greatest.) To test for pre-treatment equivalence on all outcome measures, treatment completers were evaluated for pre-treatment differences across the four treatment groups using ANOVAs for continuous data and using proportional ordered logistic regression for ordinal data.

Outcome Analyses

Proportional ordered logistic regression was used to test for the impact of PE-FMR (present or not), deepened extinction (present or not), and their interaction on the level of improvement in behavioral approach on BAT-T and BAT-G at post-treatment and follow-up. Level of improvement in behavioral approach was calculated by subtracting the highest step achieved at baseline from the highest step achieved at post-treatment and follow-up BATs. For continuous outcomes, 2x2 ANCOVAs were used to test for the impact of PE-FMR (present or not), deepened extinction (present or not), and their interaction on assessments at post-treatment and follow-up, controlling for baseline level.

Treatment Efficiency

The prediction that PE-FMR boosts the speed of fear reduction during treatment was tested by determining whether the participants with PE-FMR augmentation reached

the habituation criteria to terminate phases 1 and 2 of treatment faster than the participants without PE-FMR augmentation (phase 3 was not included in this analysis, since it was a standard length of 12 minutes for all participants). Treatment was terminated during phases 1 and 2 when participants reached a mild fear level (25 out of 100 or below) while on the most difficult step in the exposure therapy treatment hierarchy (placing one's hand flat on the bottom of an open tank containing the feared animal). When treatment was not terminated within the 40-minute maximum time limit for each phase, the participant was censored from the analyses. We used a Cox proportional hazards model to assess the likelihood of reaching the fear reduction criteria for treatment with and without PE-FMR augmentation for phases 1 and 2 of treatment. Deepened extinction augmentation will not be accounted for in this analysis since the deepened extinction manipulation occurs during phase 3 of treatment (see Figure 8). Furthermore, the total treatment duration was summed across all three treatment phases (see Figure 8) and an independent samples *t*-test was conducted to assess for differences in overall treatment duration for participants with and without retrieval.

Results

PRELIMINARY ANALYSES

Treatment Refusal

Participants were defined as refusing treatment if they completed visit 1 of the study (the screening/baseline visit) but failed to complete treatment. Frequency of treatment refusal per treatment group is included in Figure 7. Of the 164 participants randomized to a treatment condition, 34 participants (20.7%) refused treatment. Analyses suggest that treatment refusal was un-related to treatment condition ($\chi 2(3) = 2.58$, p = .46). Participants who refused treatment were slightly younger ($M = 18.81$; $SD = .90$) than those who completed treatment ($M = 19.45$; $SD = 2.04$; $t(123.42) = -2.66$, $p = .009$, equal variances not assumed). There were also no differences among those who refused versus completed treatment on fear target (i.e., snake vs. spider), gender, ethnicity, or race distribution (all p's > .12 on chi-squared tests).

Independent sample t-tests did not identify differences between participants that refused and completed treatment on questionnaire outcomes, or on fear and disgust ratings (anticipated or peak) during either treatment context or generalization context BATs (all p's ≥ .10). Proportional ordinal logistic regression indicated that participants who completed treatment demonstrated less behavioral avoidance on the generalization BAT at baseline (42 participants did not complete step 1; 44 completed step 1; 44 completed step 2) relative to those who refused treatment (17 did not complete step 1; 11 completed step 1; 6 completed step 2; proportional odds ratio = 2.18, $p = .03$). There were no statistically significant differences on behavioral performance during the treatment context BAT at baseline (proportional odds ratio = 1.69, $p = .14$).

Missing Data

A few data were missing due to experimental error during the administration of BATs (8 data points total across all three study visits; 0.1% of the treatment completer data set). Additionally, five participants were unable to return for one-week follow-up assessment (1.4% of the treatment completer data set; see Figure 7). Given the low prevalence of missing data and potential biases associated with missing data imputation, we used a pairwise deletion approach, analyzing all available data for each statistical test performed (Graham, 2009; Schlomer, Bauman, & Card, 2010).

Baseline Differences

One-way ANOVAs comparing baseline measures across the four treatment groups revealed no significant differences on questionnaire and subjective BAT ratings (anticipated fear and disgust, and peak fear and disgust) on BATs prior to treatment (all p's ≥ .12). Furthermore, proportional ordered logistic regression identified no differences on the highest step achieved on the treatment context or generalization context BAT's (all *p*'s ≥ .33).

Outcome Analyses

Means and standard deviations for outcome measures are reported in Table 10. To assess improvement in behavioral approach at post-treatment and follow-up, we first calculated the number of additional steps the participant achieved at each of these time points beyond their baseline performance (i.e., number of steps at baseline subtracted from number of steps at post, and number of steps at follow-up). Proportional ordered logistic regression models found no impact of PE-FMR, deepened extinction, or their interaction on behavioral approach during BATs in the treatment or generalization context at post-treatment or follow-up; see Table 11).

Furthermore, two-by-two ANCOVAs (controlling for ratings at baseline) found no impact of PE-FMR, deepened extinction, or their interaction on ratings of anticipated and peak, fear and disgust during the treatment context BAT or the generalization context BAT (see Table 12). Similarly, 2 x 2 ANCOVAs revealed no effects for questionnaire outcomes at follow-up (see Table 12).

Table 10: Descriptive statistics for outcome measures at baseline, post-treatment, and one-week follow-up.

		Pre		**Post**		**FU**	
	Condition	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
BAT-T AF	Exp	78.182	14.301	35.546	24.440	32.710	21.987
	Exp + PE-FMR	75.933	13.419	31.323	25.963	30.807	25.784
	Exp + DE	81.333	15.847	39.300	23.640	35.321	24.608
	Exp + PE-FMR + DE	79.472	15.376	33.806	25.719	29.257	24.398
BAT-T AD	Exp	67.879	25.478	37.515	30.141	27.000	22.017
	Exp + PE-FMR	66.500	21.817	30.548	27.057	25.387	24.587
	Exp + DE	68.433	28.521	30.833	29.680	28.286	28.721
	Exp + PE-FMR + DE	77.750	21.220	36.333	27.687	31.714	27.129
BAT-T Step	Exp	3.515	1.679	6.848	1.839	7.129	1.258
	Exp + PE-FMR	3.839	1.655	6.968	1.722	7.000	1.673
	Exp + DE	3.400	1.589	6.967	1.586	6.857	1.860
	Exp + PE-FMR + DE	3.833	1.521	6.917	1.842	7.486	1.067
BAT-T PF	Exp	70.485	17.368	17.606	17.394	17.419	16.665
	Exp + PE-FMR	64.968	18.846	16.097	21.958	17.581	22.000
	Exp + DE	71.900	20.622	22.533	20.3177	21.036	20.644
	Exp + PE-FMR + DE	65.528	20.696	18.361	20.442	16.886	18.545
BAT-T PD	Exp	64.788	26.499	17.818	21.096	18.355	20.621
	Exp + PE-FMR	61.226	25.117	13.774	21.244	15.258	20.146
	Exp + DE	60.033	30.788	17.667	23.525	19.000	26.273
	Exp + PE-FMR + DE	66.278	24.354	18.861	23.351	21.457	25.295
BAT-G AF	Exp	86.485	13.231	53.515	25.676	33.903	24.800
	Exp + PE-FMR	84.807	11.726	47.419	25.137	37.903	29.106
	Exp + DE	86.133	16.792	53.400	23.642	37.679	24.956
	Exp + PE-FMR + DE	83.750	16.902	44.500	24.694	30.886	25.279

Table 10, cont.

		Pre		Post		FU	
	Condition	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
BAT-G AD	Exp	74.485	24.700	49.515	26.822	29.387	25.082
	Exp + PE-FMR	73.323	25.869	39.097	29.348	33.258	31.176
	Exp + DE	71.533	28.385	40.533	31.101	30.964	30.357
	Exp + PE-FMR + DE	78.861	21.266	42.000	27.578	32.771	26.949
BAT-G Step	Exp	0.970	0.728	2.364	1.168	2.968	1.110
	Exp + PE-FMR	1.065	0.772	2.581	1.148	2.867	1.279
	Exp + DE	0.933	0.828	2.567	1.223	3.000	1.109
	Exp + PE-FMR + DE	1.083	0.937	2.667	1.014	3.000	1.111
BAT-G PF	Exp	78.727	17.145	36.606	23.255	22.807	23.263
	Exp + PE-FMR	75.903	19.352	37.226	27.518	26.667	27.815
	Exp + DE	78.133	20.918	40.000	24.772	25.963	25.958
	Exp + PE-FMR + DE	74.583	20.465	31.056	22.714	24.600	25.678
BAT-G PD	Exp	66.333	25.915	35.000	24.368	21.516	20.008
	Exp + PE-FMR	64.903	28.633	32.194	32.713	22.667	26.357
	Exp + DE	65.267	29.611	32.067	32.077	23.259	31.527
	Exp + PE-FMR + DE	72.806	25.075	33.389	27.114	28.171	29.806
FSQ	Exp	88.394	9.572	---	---	48.807	27.998
	Exp + PE-FMR	86.839	10.441	---	---	48.000	24.126
	Exp + DE	89.933	10.570	---	---	47.786	25.959
	Exp + PE-FMR + DE	86.167	12.235	---	---	46.000	24.546
SBQ	Exp	57.685	17.076	---	---	26.871	22.395
	Exp + PE-FMR	50.869	16.309	---	---	21.550	19.730
	Exp + DE	54.374	17.909	---	---	24.820	18.485
	Exp + PE-FMR + DE	52.473	14.723	---	---	19.967	16.323
AMDQ	Exp	40.091	6.069	---	---	29.226	10.459
	Exp + PE-FMR	36.452	6.752	---	---	27.161	10.574
	Exp + DE	36.500	7.969	---	---	25.071	9.576
	Exp + PE-FMR + DE	38.722	7.792	---	---	28.200	10.630
SEQ –	Exp	40.015	21.730	---	---	89.101	13.435
Behavioral	Exp + PE-FMR	44.323	20.392	---	---	89.629	19.112
	Exp + DE	37.008	21.224	---	---	86.460	20.483
	Exp + PE-FMR + DE	44.201	24.645	---	---	89.364	17.457

Table 10, cont.

		Pre		Post		FU	
	Condition	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
SEQ –	Exp	42.685	26.272	---	---	82.845	19.219
Anxiety	Exp + PE-FMR	52.981	22.994	---	---	85.265	20.376
	Exp + DE	49.047	29.361	---	---	85.271	16.516
	Exp + PE-FMR + DE	50.417	27.267	---	---	86.491	17.546
ACQ-S	Exp	27.212	11.776	---	---	7.807	10.173
	Exp + PE-FMR	26.903	10.672	---	---	8.968	9.318
	Exp + DE	28.133	10.890	---	---	9.750	9.842
	Exp + PE-FMR + DE	26.278	10.759	---	---	7.886	8.369

Note. BAT-T = behavioral approach test, treatment context. BAT-G = behavioral approach test, generalization context. AF = anticipated fear, rated before the BAT. AD = anticipated disgust, rated before the BAT. Step = highest step completed in the BAT. PF = peak fear, rated directly after the BAT. PD = peak disgust, rated directly after the BAT. FSQ = Fear of Snakes/Spiders Questionnaire, sum score. SBQ = Spider/Snake Belief Questionnaire, average rating. AMDQ = Armfield and Mattiske Disgust Questionnaire, sum score. SEQ – Behavioral = Self-Efficacy Questionnaire for Behavioral Approach, average rating. SEQ – Anxiety, Self Efficacy Questionnaire for Anxiety Management, average rating. ACQ-S = Agoraphobic Cognitions Questionnaire adapted for Snake/Spider Phobia, sum score. Exp = Exposure therapy. Exp + PE-FMR = Reactivation trial 25 minutes prior to beginning exposure therapy. Exp + DE = Exposure therapy with deepened extinction. Exp + PE-FMR + DE = Reactivation trial 25 minutes prior to beginning exposure therapy with deepened extinction. Pre = baseline assessment. Post = assessment immediately post-treatment. FU = one week follow-up assessment.

Table 11: Results for ordinal outcomes. Between-group differences in the highest step achieved during the BAT in the treatment and generalization contexts.

	Effect	Proportional Ordered Odds Ratio	*t*-value	*p*-value
BAT-T				
Baseline to Post Change	PE-FMR	0.814	-0.461	.645
	DE	1.280	0.550	.583
	PE-FMR x DE	0.805	-0.350	.727
Baseline to FU Change	PE-FMR	0.724	-0.710	.478
	DE	0.921	-0.179	.858
	PE-FMR x DE	1.657	0.798	.425
BAT-G				
Baseline to Post Change	PE-FMR	1.271	0.536	.592
	DE	1.445	0.807	.419
	PE-FMR x DE	0.698	-0.564	.572
Baseline to FU Change	PE-FMR	0.747	-0.647	.518
	DE	0.984	-0.035	.972
	PE-FMR x DE	1.112	0.164	.870

Note. BAT-T = behavioral approach test, treatment context. BAT-G = behavioral approach test, generalization context. DE = deepened extinction. PE-FMR = reactivation 25 minutes prior to exposure therapy. DE x PE-FMR = interaction of deepened extinction and retrieval 25 minutes prior to exposure therapy. Baseline = pre-treatment assessment. Baseline to Post Change = number of BAT steps increased from baseline to post treatment. Baseline to Follow Up change = number of steps increased from baseline to follow up. PE-FMR dummy coding (0 = no reactivation 25 minutes before treatment; 1 = reactivation 25 minutes before treatment); Deepened extinction dummy coding (0 = no deepened extinction; 1 = deepened extinction).

Table 12: Results for continuous outcomes. Two by two ANCOVAs testing the impact of treatment with and without deepened extinction, with and without reactivation 25 minutes before treatment, and their interaction, on assessment at post-treatment and one-week follow-up.

Assessment	Effect	Post-Treatment			Follow-Up		
		F	*p*	*Eta*^{2}	*F*	*p*	*Eta*^{2}
BAT-T: Anticipated Fear	DE	0.163	0.687	0.001	0.083	0.774	0.001
	PE-FMR	0.409	0.523	0.003	0.069	0.794	0.001
	DE x PE-FMR	0.009	0.926	<.001	0.205	0.652	0.002
BAT-T: Anticipated Disgust	DE	1.081	0.300	0.007	0.051	0.822	<.001
	PE-FMR	1.393	0.240	0.009	0.104	0.748	0.001
	DE x PE-FMR	0.961	0.329	0.006	0.026	0.873	<.001
BAT-T: Peak Fear	DE	0.859	0.356	0.006	0.642	0.425	0.005
	PE-FMR	<.001	0.986	<.001	0.172	0.679	0.001
	DE x PE-FMR	0.127	0.722	0.001	0.489	0.486	0.004
BAT-T: Peak Disgust	DE	0.072	0.789	<.001	0.251	0.617	0.002
	PE-FMR	0.310	0.579	0.002	0.121	0.728	0.001
	DE x PE-FMR	0.078	0.781	0.001	0.046	0.832	<.001
BAT-G: Anticipated Fear	DE	<.001	0.989	<.001	0.466	0.496	0.004
	PE-FMR	0.769	0.382	0.005	0.614	0.435	0.005
	DE x PE-FMR	0.085	0.771	0.001	1.487	0.225	0.012
BAT-G: Anticipated Disgust	DE	1.359	0.246	0.008	0.288	0.593	0.002
	PE-FMR	2.520	0.115	0.014	0.461	0.499	0.003
	DE x PE-FMR	0.613	0.435	0.003	0.531	0.468	0.004
BAT-G: Peak Fear	DE	0.383	0.537	0.003	0.313	0.577	0.002
	PE-FMR	0.093	0.762	0.001	0.700	0.405	0.005
	DE x PE-FMR	1.279	0.260	0.009	0.335	0.564	0.003
BAT-G: Peak Disgust	DE	0.139	0.710	0.001	0.197	0.658	0.001
	PE-FMR	0.104	0.748	0.001	0.093	0.761	0.001
	DE x PE-FMR	0.012	0.912	<.001	0.023	0.880	<.001
FSQ	DE	---	---	---	0.066	0.797	0.001
	PE-FMR	---	---	---	<0.00	0.986	<.001
	DE x PE-FMR	---	---	---	0.001	0.973	<.001
SBQ	DE	---	---	---	0.048	0.828	<.001
	PE-FMR	---	---	---	0.024	0.878	<.001
	DE x PE-FMR	---	---	---	0.289	0.592	0.002
SEQ – Behavioral	DE	---	---	---	0.153	0.697	<.001
	PE-FMR	---	---	---	0.027	0.869	<.001
	DE x PE-FMR	---	---	---	0.055	0.815	<.001

Table 12, cont.

Assessment	Effect	Post-Treatment			Follow-Up		
		F	*p*	*Eta*^{2}	*F*	*p*	*Eta*^{2}
SEQ –Anxiety	DE	---	---	---	0.023	0.880	<.001
	PE-FMR	---	---	---	0.001	0.967	<.001
	DE x PE-FMR	---	---	---	0.031	0.859	<.001
AMDQ	DE	---	---	---	0.299	0.585	0.002
	PE-FMR	---	---	---	0.091	0.764	0.001
	DE x PE-FMR	---	---	---	0.056	0.812	<.001
ACQ-S	DE	---	---	---	0.720	0.398	0.004
	PE-FMR	---	---	---	0.409	0.523	0.002
	DE x PE-FMR	---	---	---	0.691	0.407	0.004

Note. BAT-T = behavioral approach test, treatment context. BAT-G = behavioral approach test, generalization context. BAT-T = behavioral approach test, treatment context. BAT-G = behavioral approach test, generalization context. AF = anticipated fear, rated before the BAT. AD = anticipated disgust, rated before the BAT. Step = highest step completed in the BAT. PF = peak fear, rated directly after the BAT. PD = peak disgust, rated directly after the BAT. FSQ = Fear of Snakes/Spiders Questionnaire, sum score. SBQ = Spider/Snake Belief Questionnaire, average rating. AMDQ = Armfield and Mattiske Disgust Questionnaire, sum score. SEQ – Behavioral = Self-Efficacy Questionnaire for Behavioral Approach, average rating. SEQ – Anxiety, Self Efficacy Questionnaire for Anxiety Management, average rating. ACQ-S = Agoraphobic Cognitions Questionnaire adapted for Snake/Spider Phobia, sum score. DE = deepened extinction. PE-FMR = reactivation 25 minutes prior to exposure therapy. DE x PE-FMR = interaction of deepened extinction and retrieval 25 minutes prior to exposure therapy.

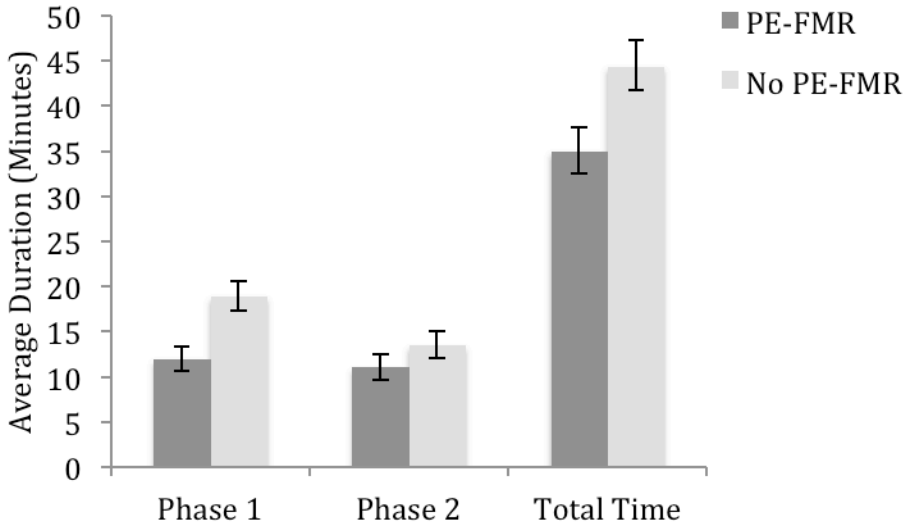
TREATMENT EFFICIENCY

Participants were coded as censored if they did not reach the fear reduction criteria during the 40-minute maximum duration of phase 1 and phase 2 of treatment. During phase 1, 17 participants (13.08%) did not reach the fear reduction criteria (n = 11 and n = 6 in exposure without and with PE-FMR, respectively); and during phase 2, 13 participants (10%) did not reach the fear reduction criteria (n = 6 and n = 7 in exposure without and with PE-FMR, respectively).

A cox proportional hazards analysis revealed that participants completing exposure augmented with PE-FMR reached the fear reduction criterion more rapidly during phase 1 of treatment (B = .56, p = .003; Cox proportional hazard ratio = 1.75), but not during phase 2 of treatment (B = .22, p = .23; Cox proportional hazard ratio = 1.25). These findings suggest that at any time-point during phase 1 of treatment (exposure to the first snake or spider the participant encountered), participants with PE-FMR augmentation were nearly twice as likely to reach fear reduction criteria than those without PE-FMR augmentation.

Including all participants (adding in those censored in the survival analysis) and all three phases of exposure therapy, PE-FMR augmentation resulted in a 21.16% reduction in total treatment duration on average (treatment duration with PE-FMR, M = 34.99 minutes, SD = 20.94; treatment duration without PE-FMR, M = 44.38 minutes, SD = 22.25; $t(128) = 2.48$, p = .01; see Figure 9).

Figure 9: Average duration (in minutes) of phases 1 and 2 of treatment and total duration of treatment (including the 12 additional minutes from phase 3).



Note. PE-FMR = Pre-extinction fear memory reactivation.

Discussion

The primary aim of the present study was to test the independent and combined efficacy of PE-FMR and deepened extinction for improving exposure therapy outcomes in a large sample of participants with naturally acquired fear. The primary hypotheses that PE-FMR and deepened extinction would enhance exposure therapy, alone and in combination, were not supported by the data. Neither PE-FMR nor deepened extinction influenced overall outcomes on behavioral approach tests or questionnaires at post-treatment or one-week follow-up. However, analyses confirmed the secondary hypothesis, demonstrating that PE-FMR augmentation produced more rapid fear reduction during treatment. Specifically, those in the PE-FMR group reached the criteria for fear reduction (and termination of the treatment phase) more rapidly during phase 1 of exposure therapy (exposure to the first snake/spider encountered during treatment). Furthermore, because exposure therapy duration was individually tailored based on speed of fear reduction, those with the PE-FMR augmentation received a lower dose of exposure therapy. Even with 21% less time in exposure therapy on average, those with the PE-FMR augmentation had equivalent overall outcomes at post-treatment and follow-up.

These findings corroborate prior data (Telch et al., 2017) in demonstrating that PE-FMR boosts the speed of fear extinction. The present data provide an excellent complement to prior research, strengthening confidence in this finding, in part because of the use of different types of control groups across studies. The control group in Telch et al. (2017) completed the reactivation procedure directly after the last exposure therapy trial. This had the benefit of producing equivalent duration of exposure to the feared animal across groups, while ensuring that only the PE-FMR augmentation group (which

received reactivation 30 minutes before treatment) completed exposure therapy within the 6-hour reconsolidation update window. However, the use of this procedure in the control group had the drawback of limiting the strength of the interpretation of the finding that PE-FMR produced more rapid reduction of fear. Since the PE-FMR group received reactivation prior to treatment, and the control group completed this procedure directly after treatment, the control group had less overall time with the feared stimulus prior to beginning treatment. One could therefore argue that the PE-FMR augmentation group in this study may have displayed lower fear during the first third of treatment only because this group had more exposure to the feared stimulus (in the form of the 10 second reactivation trial) prior to beginning treatment (giving this group a head start for treatment). In the present study, however, the control group completed the reactivation procedure at the end of their baseline visit. This ensured equivalent duration of time with the feared animal prior to initiating exposure therapy, strengthening confidence in the conclusion that PE-FMR produces more rapid fear reduction during exposure therapy. Furthermore, we extended this finding in the present study by demonstrating that treatment can be terminated earlier when more rapid fear reduction occurs in the PE-FMR group, with equivalent results being maintained at post-treatment and one-week follow-up assessment.

In regard to the null findings for the primary study hypotheses, several aspects of the present study increase the probability that null effects represent a true absence of between-group differences rather than a type II error. First, the large sample sizes in the present study (between 28 and 35 participants in each of the four treatment groups at follow-up; and 59+ participants per group when analyzing the main effects of PE-FMR or deepened extinction) increase the statistical power to identify between group differences as compared with prior studies (15 to 17 per group in Telch at al., 2017 and Shiban et al.,

2015), which reduces the likelihood that null effects were related to sampling error or underpowered analyses.[6] Furthermore, descriptive statistics demonstrate sufficient variance at all time points on continuous outcome measures, suggesting that null findings were not due to restricted variance in assessments or due to ceiling effects (see Table 10). Similarly, after treatment completion, only about two-thirds of the sample reached the maximum step on BAT-T (62.31% at post and 64.00% at follow-up), and less than half of the sample completed the maximum step on BAT-G (21.54% at post and 41.46% at follow-up obtaining the most challenging step) suggesting that a lack of differences on behavioral outcomes was also unrelated to a ceiling effect. Together, the statistical power to detect between-group differences due to the relatively high sample size, combined with the absence of ceiling effects for all except one outcome measure, increase confidence that null findings reflect a true absence of between-group differences in the present study.

The finding that PE-RFM did not boost exposure therapy outcomes corroborates results from Shiban et al. (2015), although the present study included a larger sample size and used an in vivo PE-FMR, rather than a virtual reality PE-FMR. The findings contrast with results of Telch and colleagues (2017) who found that PE- FMR produced lower fear responding in a generalization test at one-month follow-up. It is possible findings differed from Telch and colleagues due to procedural differences between the studies. For example, relative to the design of Telch et al. (2017), the BAT-generalization procedures in the present study provided more changes from the treatment context. Comparing the treatment procedure to the generalization test, Telch and colleagues changed the animal used (using animals of distinctly different colorations) and changed the set-up of the

[6] We conducted an a-priori power analysis for the two-tailed ($\alpha = .05$), 2x2 ANCOVAs used in the primary outcome analyses, and found that we would have 78% likelihood of detecting main effects (and a 61% likelihood of detecting an interaction) of a medium effect size ($f = .25$) with a total sample size of $N = 120$.

room (changing the color and fabric of the floor mat). However, during the generalization test, participants performed the same task completed during treatment (i.e., standing barefoot within 1-foot of the feared animal). In contrast, in the generalization test in the present study, the animal was changed, the set up of the room was changed (participants approached an animal held by a researcher rather than approaching an animal in an open tank), and the tasks participants performed were also changed (see Methods section for details). Due to the change in the hierarchy of behavioral tasks in addition to the change in animal and change in room set-up, the present study may have provided a more stringent test of treatment generalization.

Telch et al. (2017) and the present study also differ in the time periods used for follow-up assessment, which may have contributed to the discrepant findings. Telch et al. used a one-month follow-up whereas the present study used a one-week follow-up. It is possible that differences between participants with and without PE-FMR may have emerged in the present study if a follow-up assessment had been conducted at a later time point. However, questionnaire assessment at six-month follow-up (although probably less sensitive than behavioral tests) did not identify differences in participants with and without PE-FMR in a prior study (Shiban et al., 2015). Furthermore, the use of self-report ratings throughout treatment during the present study may have served as a distraction during treatment, creating a cognitive load that may have interfered with treatment (e.g., Telch et al., 2004) and perhaps obscuring the long-term benefits of PE-FMR identified by Telch and colleagues (2017). On the other hand, some research suggests that discussion related to exposure therapy, such as labeling of emotions, does not interfere with treatment outcomes and produces better outcomes than distraction during treatment (Kircanski, Lieberman, & Craske, 2012).

Differences in dosage of exposure therapy may offer another explanation for the differing effects of PE-FMR across studies. Both the present study and Shiban et al. (2015) provided a larger treatment dose (over an hour total treatment time on average in Shiban et al., and up to 92 minutes with length tailored to fear reduction in the present study), whereas Telch and colleagues provided a standardized, 18-minute exposure therapy protocol to all participants. It is possible that the benefits of PE-FMR, in the context of an already potent intervention within the specific phobia population (Őst, 1989), were only evident with a reduced dosage of exposure therapy. Furthermore, if treatment length had been equivalent in the present study, it is possible that further benefits may have been evident at follow-up in the PE-RFM group. On the other hand, the tailored length of treatment provides greater generalizability of findings, as treatment is typically terminated in standard practice after the achievement of significant fear reduction. Additionally, the increased dosage of treatment in the present study is closer to the average reported length of specific phobia treatment when administered in a clinical setting (reported as 2.1 hours in prior one-session exposure-based specific phobia treatment; Őst, 1989), again promoting generalizability of findings from the present study to clinical settings.

Furthermore, since the procedures for PE-FMR itself differed between the present study and Telch et al. (2017), perhaps the PE-FMR trial in Telch et al. triggered the reconsolidation update mechanism whereas the procedure used in the present study did not. Findings from rodent models suggest that qualities of the fear memory, such as it's age or the strength of reinforcement history (Alberini & LeDoux, 2013), and qualities of the reactivation trial, such as the level of prediction error invoked (Sevenster, Beckers, & Kindt, 2013), each influence susceptibility of a particular memory to reconsolidation. Thus, the optimum length or parameters of the reactivation trial may differ across

individuals and across particular fear memory structures. A promising direction for future research would involve identification of biomarkers (e.g., differing patterns of neural activity on fMRI) during PE-FMR that indicate the initiation of reconsolidation update rather than inhibitory learning, such that the specific procedure and duration of the PE-FMR can be tailored to the individual patient.

There are additionally several possible explanations for the failure of the deepened extinction to augment exposure therapy outcomes. First, it may simply suggest that findings in animal (Rescorla, 2006) and human (Culvier et al., 2015) fear conditioning and extinction paradigms do not extend to the extinction of naturally acquired fear. Additionally, whereas Rescorla and Wagner (1972) suggest that presenting two feared stimuli simultaneously should produce a summation of fear responding (boosting prediction error and thus boosting the potency of learning), it is possible that the presentation of both stimuli simultaneously was simply viewed as a new context (more in line with the configrual processing theory presented by Pearce, 1987). Processing the two feared stimuli as one new context rather than an additive summation of elemental stimuli may produce the effect of varying the context of exposure therapy, but would not necessarily boost prediction error to deepen extinction (as predicted by Rescorla and Wagner, 1972). Although prior research has demonstrated that context variation boosts the potency of fear extinction learning (e.g., Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Rodriguez, Craske, Mineka, & Hladek, 1999), it is possible that presenting two snakes/spiders simultaneously, even if processed as an additional context, does not produce meaningful improvement over exposure to two different snakes or spiders individually (i.e., two versus three exposure therapy contexts).

Furthermore, it is possible that deepened extinction was unsuccessful as an augmentation strategy due to limited resources to fully attend to both feared stimuli

simultaneously. Although the two animals (spiders or snakes) were in adjacent tanks during the deepened extinction procedure, it is possible that participants were visually focusing on only one animal at a time. Prior studies in the extinction of laboratory-conditioned fear, in contrast, have used mixed sensory modalities to reduce the potential for completing attentional resources (i.e., use of an auditory stimulus (tone) as one cue and a visual stimulus (light) as the second cue; Jones, Ringuet, & Monfils, 2013; Rescorla, 2006). Future studies could examine deepened extinction using feared cues in separate sensory modalities, for example, combining exposure to an audio recording of a trauma narrative alongside trauma-related olfactory cues for PTSD, or exposure to a crowded mall after ingestion of caffeine for panic disorder with agoraphobia.

When interpreting findings from this study, it is important to note several strengths and limitations. Limitations include the use of a population primarily drawn from non-treatment seeking undergraduate psychology students. It will be important to extend findings, particularly the observation that PE-FMR may facilitate the speed of fear reduction, to treatment seeking populations, and to the multi-session exposure therapy protocols typically used for other anxiety disorders (e.g., Craske & Barlow, 2007; Foa, Hembree, & Rothbaum, 2007; Kozak & Foa, 2004). It is unclear whether repeatedly using PE-FMR across multiple treatment visits would produce sustained benefits in terms of more rapid within-session fear reduction during each session, and perhaps also translate to the need for less treatment visits overall for multi-session treatment protocols. Furthermore, the relatively short follow-up period (approximately one-week), and the high dose of exposure therapy (up to 92 minutes) relative to prior exposure therapy augmentation studies (e.g., 18 minutes in Telch et al., 2017), may have limited our ability to detect the influence of the augmentation strategies tested. On the other hand, the higher dose of exposure therapy increases generalizability of findings to clinical settings. In

contrast, a notable strength of this study was the relatively high statistical power for detecting differences between groups due to the large sample size. The high statistical power increases confidence that null findings represent a true similar between groups, rather than a failure to detect differences due to sampling error.

This study suggests several potential avenues for future research. First, it may be useful to produce conceptual replications of the null effect of deepened extinction to determine whether the null findings in the present study may have been an artifact of the specific procedures or population used in this study. These replications will be necessary to conclude with more confidence that the augmenting effects of the deepened extinction procedure observed in extinction of laboratory-conditioned fear do not extend to extinction of naturally acquired fears. Furthermore, it will be critical to test the potential utility of PE-FMR for boosting speed of fear reduction within a treatment seeking population and across multi-session treatment protocols. This will be critical for determining whether the 21% reduction in overall treatment duration observed in the present study could translate to shorter treatment visits, and perhaps fewer treatment visits, in the context of implementing multi-session exposure therapy protocols within treatment-seeking populations.

GENERAL DISCUSSION

More than one-fourth of the general population will meet criteria for an anxiety-related disorder at some point in their lifetime (Kessler et al., 2005). These disorders are associated with reduced quality of life (Mendlowicz & Stein, 2000), work impairment (Greenberg et al., 1999), increased risk for physical disorders and disability (Sareen, Cox, Clara, & Asmundson, 2005), increased risk for comborbid psychological disorders (Grant et al., 2004; Wittchen et al., 2000), and suicidal ideation and attempts (Sareen et al., 2005). Anxiety-related disorders share the common element of pathological fear responding, which can be defined as fearful responding in a situation in which this response is not protective, but instead is either unnecessary or unhelpful to such an extent that it causes significant distress or interference with daily life.

Decades of research have been geared toward identifying factors that contribute to the development and maintenance of the pathological fear associated with anxiety disorders, in an effort to facilitate its prevention and treatment (e.g., Butler, Chapman, Forman, & Beck, 2006; Hoffman & Mathew, 2008). However, a substantial proportion of patients (estimates ranging from 15 to 40%; Clark et al., 2006; Foa et al., 1999; Foa, Liebowitz et al., 2005; Ladouceur et al., 2000; Telch et al., 1993) do not respond to gold-standard treatments such as cognitive-behavioral therapies. It is therefore of critical importance that researchers seek a better understanding of the factors that govern increases and decreases in pathological fear to improve prevention and treatment strategies. The studies in this dissertation align with this overarching goal. Study 1 examined contributors to the development of pathological fear (i.e., PTSD symptoms) after exposure to environmental stress. Study 2 examined the role of safety behaviors in interfering with the reduction in pathological fear during exposure therapy, a treatment

technique commonly employed across gold-standard treatments for anxiety disorders (Foa, Hembree, & Rothbaum, 2007; Kozak & Foa, 2004; Heimberg & Becker, 2002). Finally, study 3 examined the role of novel behavioral strategies (pre-extinction fear memory reactivation and deepened extinction) in facilitating reductions in pathological fear during exposure therapy.

Overview of Study Findings and Implications

Specifically, study 1 tested whether threat perception was associated with increases in pathological fear (i.e., PTSD symptoms) above and beyond the level of stress exposure, itself. To achieve this aim, soldiers reported on their level of stress exposure, appraisal of stress exposure (threat perception), and psychological reactions (PTSD and depression symptoms) during deployment to a warzone. Soldiers with above average threat perception (+1 *SD*) experienced increases in PTSD symptoms as a function of increases in stress exposure. However, Soldiers with below average threat perception (-1 *SD*) experienced no increase in PTSD symptoms as a function of stress exposure. Threat perception, but not stress level, was positively correlated with depression symptoms, a condition commonly comorbid with PTSD (Campbell, Felker, Liu, & Yano, 2007).

Combined with prior longitudinal research, results from study 1 strengthen confidence in the causal role of perceived threat in the development of PTSD. Whereas prior studies have assessed threat perception by measuring it months, or even years, after return from military deployment (e.g., D. W. King et al., 1995; Renshaw, 2011), this study assessed threat perception during deployment, which decreases the influence of retrospective biases. In addition to reduction in the time lapse, the greater similarity between the context in which the stressor was experienced and reported, likely improves the accuracy of the report (Grant et al., 1998).

Although the design of study 1 limits the strength of causal inference because threat exposure and appraisal were measured simultaneously, prospective data suggests that threat-related biases, as reflected on more experimentally controlled (although less generalizable) laboratory tasks, are associated with later increases in fear reactivity (Beevers, Lee, Wells, Ellis, & Telch, 2011; Muris, Huijding, Mayer, & Hameetman,

2008). Combining results across studies, data provide a strong case for the causal role of threat perception in the development of pathological fear. These findings thus lend further weight to cognitive behavioral models of pathological fear, which emphasize the causal role of perception in influencing behavioral (e.g., avoidance) and emotional (e.g., fear) responses (Beck, Emery, & Greenberg, 2005).

Given this knowledge, it is possible that shortly after exposure to a given precipitating environmental stressor, there may be a measurable increase in related and overgeneralized threat appraisals among those most at risk for the development of PTSD. In future studies, it would be useful to obtain enough assessments to provide the statistical power necessary to do a cross-lagged model, to ascertain whether an increase in threat perception in response to a given environmental stressor prospectively predicts subsequent increases in pathological fear (i.e., PTSD symptoms). Furthermore, given the stigma associated with self-report of symptoms, particularly among populations such as military personnel and first responders, who are often at increased risk for the development of psychopathology (e.g. Benedek, Fullerton, & Ursano, 2007; Berninger, Webber, & Niles, 2010; Smith et al., 2008), it would be useful to assess increases in threat perception by using implicit, rather than self-report, assessments (e.g., assessing bias in interpretation of ambiguous sentences; Eysenck, Mogg, May, & Richards, 1991). Identifying higher-than-average threat perception tendencies (either as a pre-dispositional risk factor, or as an early marker of pathological reactivity to stress exposure) could be used as a signal to deploy preventative interventions, such as closer symptom monitoring and interventions to correct overgeneralized threat perception. Evidence in experimental paradigms suggests that increasing or decreasing threat interpretation bias through brief computer-based interventions can respectively increase or decrease avoidance behavior (Lester, Field, & Muris, 2011; Menne-Lothmann et al., 2014; Muris, Huijding, Mayer, &

Remmerswaal, 2009). Thus, modifying threat interpretation biases in those most at risk for developing PTSD could reduce avoidance behavior, one of the primary risk factors for the development of PTSD (Dunmore, Clark, & Ehlers, 2001).

Whereas study 1 examined factors that contribute to the development of pathological fear, study 2 examined a manipulation that may interfere with the reduction of pathological fear during treatment. Specifically, study 2 used meta-analytic methods to investigate the influence of adding or removing safety behaviors (i.e., unnecessary protective actions) on exposure therapy outcomes. Over the last decade, there has been a plethora of qualitative syntheses of studies describing the influence safety behavior use on exposure therapy (Blakey & Abramowitz, 2016; Goetz, Davine, Siwiec, & Lee, 2016; Helbig-Lang & Petermann, 2010; Parrish, Radomsky, & Dugas, 2008; Rachman, Radomsky, & Shafran, 2008; Telch & Lancaster, 2012). Whereas some of these reviews concluded that safety behavior use during exposure therapy would produce deleterious effects and cautioned against their use (Blakey & Abramowitz, 2016; Helbig-Lang & Petermann, 2010; Telch & Lancaster, 2012), others suggested that using safety behaviors judiciously could improve exposure therapy outcomes (Rachman et al., 2008).

The only meta-analysis conducted to date produced inconclusive results regarding the impact of safety behaviors on exposure therapy outcomes, and identified moderate to high variability among study effect sizes (Meulders, Van Daele, Volders, & Vlaeyen, 2016). This meta-analysis was marked by a number of methodological weaknesses, such as (a) examining only one outcome measure (subjective fear ratings) at one time point (the last available time point); (b) inclusion of several studies that employed a within subjects, crossover design, which increases the risk for carryover effects of learning-based interventions such as safety behavior use/fading; (c) inclusion of assessments during which groups were not equated for safety behavior use during the evaluation (e.g.,

one group had instructions to use safety behaviors, and the other did not, when providing fear ratings); and (d) use of a somewhat restrictive use literature review, searching for studies with an explicit mention of safety behaviors rather than including a broader category of search terms conceptually related to safety behaviors (e.g., distraction, response induction aids, etc.). Therefore, study 2 in this dissertation describes a follow-up meta-analysis, with the primary aim of re-evaluating the overall effects of adding and removing safety behaviors during exposure therapy, and with the secondary aim of evaluating moderators for any remaining variability in study effects sizes.

For the overall effects in study 2, we found that removing safety behaviors produced moderately superior outcomes (g = .44), and adding safety behaviors did not impact outcomes. However, there was a significant degree of variability in SB+ study effect sizes. With further analyses, we identified that the treatment target of exposure therapy moderated the impact of adding safety behaviors, such that exposure therapy targeting specific phobia produced a small, but statistically significant, reduction in treatment response (g = .12).

These findings suggest that clinicians should seek to remove safety behaviors over the course of exposure therapy to achieve better outcomes, and suggest that the addition of safety behaviors detracts from the efficacy of exposure therapy for specific phobia symptoms. However, with the exception of two studies, the procedures in all SB+ studies involved maintaining safety behaviors throughout exposure therapy, as opposed to introducing and then fading them over the course of treatment. This procedure, of maintaining safety behaviors throughout treatment, contrasts markedly with the recommendations provided by Rachman and colleagues (2008) for the judicious use of safety behaviors. Specifically, they recommend that safety behaviors "should be used in a limited manner and only for a limited period, especially in the early stages of treatment...

[and] once the patient is thus engaged, the pace of the treatment can be raised, and the safety behavior and safety gear can be (gradually) dispensed with," and later in treatment "if an obstacle is encountered…the tactical use of safety behavior can remove the barrier and then be tapered off" (p. 171). In line with the original recommendations of Bandura, Jeffery, and Wright (1974) in the context of guided mastery treatment, safety behaviors are recommended as strategies to induce approach behavior, with the caveat that they should then be removed during treatment. Since the vast majority of SB+ studies did not use this procedure (and instead maintained safety behaviors throughout treatment) there is still very little data on the potential benefits or drawbacks of judicious safety behavior use. It is noteworthy that the only two SB+ studies that followed the judicious use procedure (introducing, and then fading, SBs) found no between group-differences; outcomes were equivalent with and without judicious safety behavior use during exposure therapy (Deacon et al., 2010; Antony et al., 2001). However, additional replications testing the judicious use of safety behaviors are needed in order to justify the development of clinical guidelines.

A careful review of the literature furthermore reveals a number of factors that should be considered when interpreting findings of studies that have experimentally manipulated safety behaviors, especially in the presence of null findings. Our review demonstrates that null findings have been more prevalent among SB+ studies as opposed to SB- studies. Thus, many SB+ studies have concluded that adding safety behaviors has no deleterious impact on exposure therapy outcomes. However, this interpretation must be made with a great deal of caution for a number of reasons. Primarily, findings from our meta-analysis suggest that non-equivalent testing conditions (i.e., conditions in which the groups differed regarding access to safety behaviors during the assessment of fear or other outcomes) may be contributing to the overall null findings. Specifically, we found

that the equivalence of testing conditions moderated the effect sizes observed in SB+ studies, such that when testing conditions were non-equivalent, symptom scores were lower in the treatment condition that had access to safety behaviors. These lower symptom scores may not necessarily generalize to encounters with the feared situation in a real-world environment, when safety behaviors may not be available for use.

In addition to non-equivalent testing conditions, the characteristics of most SB+ studies in the literature may make it more challenging to detect the influence of adding safety behaviors on treatment outcomes. First, the use of non-treatment seeking samples with relatively low clinical severity may produce a floor effect for exposure therapy. Second, the use of relatively short durations of exposure therapy in several of the studies could be insufficient for achieving adequate treatment response, which would make any influence of the safety behavior manipulation on treatment response more difficult to detect. Third, the majority of studies have evaluated the influence of safety behaviors selected by investigators rather than participants. However, safety behaviors are more accurately defined by an analysis of the function of a given behavior for an individual (Helbig-Lang & Petermann, 2010; Telch & Lancaster, 2012). Allowing participants to select their own safety behaviors would likely lead to stronger influences of the behavior on treatment outcomes because this would remove the guess work of investigators selecting a safety behavior that may or may not match the participant's core threat. Furthermore, allowing participants to select their own safety behaviors would better mirror the types of safety behavior adaptations that would be occurring in clinical settings. Future studies that account for these methodological concerns would greatly contribute to the literature on safety behavior use in exposure therapy.

Due to the experimental nature of the manipulations in study 2, combined with the finding that removing safety behaviors had a robust and consistent benefit for enhancing

treatment outcomes relative to standard exposure therapy, findings lend weight to the conclusion that safety behaviors play an important role in maintaining pathological fear. This result provides a potential explanation for how some individuals can maintain pathological fear, despite repeated confrontations with the feared situation(s) in daily life. We would predict that individuals who use safety behaviors (or have them available for use) during these encounters would maintain some level of pathological fear over time, despite regular encounters with the feared situation. There are several potential mechanisms by which safety behaviors maintain fear, for example, blocking threat disconfirmation and reducing attentional resources. Further research is needed to determine the mechanisms by which safety behavior use may maintain fear during exposure therapy (for an example of one such study, see Telch and Plasencia, 2010, as cited in Telch & Lancaster, 2012).

Whereas study 2 examined the role of safety behaviors in maintaining pathological fear during exposure therapy, study 3 examined the use of two novel behavioral strategies for boosting pathological fear reduction during exposure therapy: pre-extinction fear memory reactivation (PE-FMR) and deepened extinction. Each of these strategies has been translated form basic science research in animal models (Monfils, Cowansage, Klann, & LeDoux, 2009; Rescorla, 2006) and human models of fear conditioning and extinction (Culver, Vervliet, & Craske, 2015; Schiller et al., 2010). PE-FMR is hypothesized to improve the efficacy of exposure therapy through the reconsolidation update mechanism. Specifically, according to prior research (Monfils et al., 2009; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013), adding PE-FMR to exposure therapy should ensure that the new information gained during treatment updates the original fear memory, rather than creasing a second, context dependent memory that competes with the original memory for expression.

Deepened extinction, on the other hand, is hypothesized to facilitate treatment by increasing prediction error (i.e., increasing the discrepancy between anticipated and actual occurrences of the feared outcome). Prediction error tends to reduce over the course of treatment, potentially leading to asymptotic benefits over the course of treatment. However, the deepened extinction procedure, in which fear responding to each of two stimuli is extinguished independently and then simultaneously, would be predicted to increase prediction error over the course of treatment, potentially facilitating treatment outcomes (Leung & Westbrook, 2008). Specifically, the elemental model of associative learning (Rescorla & Wagner, 1972) would predict that the associations of the two stimuli would combine additively when they are presented simultaneously, producing a greater prediction error and greater treatment response.

Contrary to prediction, however, in study 3, neither PE-FMR nor deepened extinction led to greater reductions in pathological fear responding at post-treatment or one-week follow-up. This study represents the first experimental trial testing deepened extinction (DE) as a strategy for enhancing exposure therapy. Due to the large sample size (e.g., approximately 60 participants with and without DE), it is unlikely that the null finding was related to low statistical power to detect effects. (A priori power analyses suggest that there was only a 20% likelihood that we would have failed to detect a moderate-size effect, using a standard, two-tailed alpha level of .05.) However, further conceptual replications of this null finding are indicated, to rule out the possibility that null effects are specific to the procedure employed in this study. For example, DE was operationalized by the presentation of two feared animals (individually and then simultaneously), whereas in prior animal models, DE has involved the presentation of a tone and a light that were each associated with a shock (Rescorla, 2006). Since the animal models used two different sensory modalities, it is possible that a similar intervention in

humans would be more efficacious. Using two separate sensory modalities may increase the ease of attending simultaneously to both stimuli, as opposed to the procedures used in study 3, which involved the more challenging task of attending to and tracking the movement of two visual stimuli simultaneously (i.e., two feared animals in separate tanks).

Assuming the null findings for deepened extinction hold upon replication, findings present theoretical implications for the processing of feared stimuli. Results may provide evidence in favor of the configural processing model as opposed to the additive processing model of feared stimuli. Specifically, the additive model would suggest that threat prediction would increase additively when two feared stimuli are presented simultaneously (Rescorla & Wagner, 1972), which in turn would deepen extinction learning. However, the configural model would suggest that the two stimuli together would simply be processed as a completely new context, relative to the presentation of each of the two stimuli independently (Pearce, 1987). Consistent with study findings, the configural model would predict no augmentation effect for deepened extinction, when fear responses were only tested in the context of presenting a single feared animal (as they were in study 3). It may be useful for future studies of deepened extinction to incorporate a behavioral test with both animals (i.e., a two-stimulus test). The configural processing model would predict superior performance with DE augmentation in a two-stimulus test, but not a one-stimulus test; whereas the additive model would predict superior performance both the behavioral tests (two-stimulus and one-stimulus tests).

In regard to the effects of PE-FMR, data across studies (Telch et al., 2017; study 3) are converging to suggest that PE-FMR produces more rapid fear reduction during exposure therapy. Because study 3 provided a conceptual, rather than exact, replication of Telch and colleagues, results increased confidence in the robustness of this finding. Study

3 furthermore expanded findings from Telch and colleagues by demonstrating that we can end treatment early, when fear reduces more rapidly after PE-FMR augmentation, while maintaining equivalent outcomes through one week follow up on behavioral and questionnaire measures. The methods of study 3 thus strengthened the evidence that PE-FMR can be used to improve the efficiency of exposure therapy.

Furthermore, findings at post-treatment (either directly after, or one day after, treatment) were consistent across study 3, Telch and colleagues (2017), and Shiban and colleagues (2015), in that no studies to date have found a benefit of PE-FMR at post-treatment assessment. Although Telch and colleagues (2017) identified a benefit of PE-FMR augmentation at one-month follow-up (i.e., lower fear reported during a generalization test), study 3 found no benefits of PE-FMR augmentation during the generalization test at one-week follow-up. Together, these data suggest that the benefits of PE-FMR may take longer (at least one month) to emerge.

Alternatively, it is also possible that it is also possible that procedures used by Telch and colleagues (2017) successfully activated the reconsolidation update mechanism, whereas the procedures used in study 3 did not. This would raise questions regarding boundary conditions of initiating reconsolidation update as opposed to inhibitory learning mechanisms. Between studies, procedural differences in the FMR procedure include duration (10 seconds in Telch and colleagues and 20 seconds in study 3), and how imaginal elements were incorporated (including recall of a real or imagined encounter during the first half of FMR in study 3, and during the entire FMR procedure in Telch and colleagues). Differences in the exposure therapy protocols might also have contributed to discrepant outcomes at follow-up. Differences in the exposure therapy procedures between the Telch and colleagues as compared with study 3 include: (a) approaching a feared animal on the floor versus approaching a feared animal in a tank;

(b) a multi-step (graduated) versus one-step (flooding) exposure procedure; (c) using an un-tailored versus tailored length of treatment, and (d) assessing fear levels during versus after exposure therapy trials.

Furthermore, differences in the content of the activity during the break period after FMR and prior to exposure therapy could influence mechanisms of inhibitory learning versus reconsolidation update. Participants Telch and colleagues (2017) answered unrelated questions from a questionnaire, whereas participants in study 3 watched a re-run of a comedy television show during this break period. Each of these procedures was designed to prevent rumination on the feared stimulus (e.g., spider or snake) during the break period. This was done to better equate human models with rodent models, to reduce the anticipatory processing that might occur in human studies but not rodent studies. However, it is possible that the content of the break period has an influence on the activation of inhibitory versus reconsolidation update mechanisms.

Additionally, evidence from animal models suggests that the boundary conditions of reconsolidation update may differ based on aspects of a particular fear memory, such as its strength or age (Alberini & LeDoux, 2013). Therefore, it may be necessary to tailor procedures to the individual to target the appropriate conditions for initiating reconsolidation update rather than inhibitory learning. This would require a real-time, direct measurement of learning mechanisms within the brain, through techniques such as fMRI, to enable tailoring of the procedures to biomarkers of reconsolidation as opposed to inhibitory learning (e.g., Schiller et al., 2013). This option is financially prohibitive at this point in time, but more cost efficient strategies for observing neural mechanisms are developing rapidly (e.g., functional near infrared spectroscopy), and it may be more feasible in the future.

In addition to raising questions regarding the boundary conditions of reconsolidation update, studies suggest that PE-FMR could be operating through fundamentally different mechanisms in exposure therapy studies (e.g., study 3; Shiban et al., 2015; Telch et al., 2017) than it did in studies with rodents (e.g., Monfils et al., 2009). Specifically, animal models have found differences in fear renewal and spontaneous recovery of fear after exposure treatment with and without PE-FMR (Baker, McNally, & Richardson, 2013; Monfils et al., 2009). In contrast, follow-up tests in the human studies, examining the impact of PE-FMR on exposure therapy for specific phobias, provide little evidence of an increase in fear from post-treatment to follow-up, but rather show continued fear reduction among renewal and spontaneous recovery tests at follow-up relative to post-treatment (Study 3; Shiban et al., 2015; Telch et al., 2017). Although this hypothesis would require additional exploration, it is possible that exposure therapy in human models differs from rodents in that it may already include more of a combination of reconsolidation update and inhibitory learning, even without the addition of a structured PE-FMR trial. It is likely that people anticipate, and perhaps imagine, exposure therapy leading up to the experimental session, thus potentially providing at least one form of reactivation (i.e., imaginal) for all participants prior to exposure therapy. This hypothesis, if confirmed, may explain the observed return of fear in animal models that is less consistently found in exposure treatments for naturally acquired pathological fear in humans.

Furthermore, two human studies have shown evidence of more rapid fear reduction during treatment among those with PE-FMR (Telch et al., 2017; Study 3) whereas rodent studies do not (Baker et al., 2013; Monfils et al., 2009). This raises the question of whether the potential benefits of PE-FMR for enhancing exposure therapy are related to alterative mechanisms, in addition to reconsolidation update. Reconsolidation

update theory would predict greater resilience against return of fear, but would offer no ready explanation for more rapid fear reduction.

Evidence in animal models suggests that PE-FMR activates glutamate receptors in the amygdala (Monfils et al., 2009), similar to pharmacological enhancers such as D-cycloserine (DCS; Hofmann, Smits, Asnaani, Gutner, & Otto, 2011), which also boost the speed of fear reduction during treatment (Norberg, Krystal, & Tolin, 2008). However, PE-FMR offers a non-pharmacological alternative to boosting the speed of fear reduction, which provides several benefits. First, using behavioral as opposed to pharmacological augmentation reduces logistical barriers for therapists in the community implementing the intervention (i.e., no need to collaborate with psychiatrists). Additionally, using pharmacological enhancers may introduce the possibility that participants could attribute improvements to the drug (Powers, Smits, Whitley, Bystritsky, & Telch, 2008), which may negatively impact self-efficacy and generalization of treatment.

Integration of Findings

Studies included in this program of research produced several key findings related to factors that influence the onset and reduction of pathological fear. Study 1 demonstrated the role of heightened threat perception in facilitating the onset of pathological fear (i.e., PTSD symptoms) during exposure to environmental stress; study 2 highlighted the role of safety behaviors in blocking the reduction of pathological fear during exposure therapy; and study 3 demonstrated the role of PE-FMR in facilitating the speed of pathological fear reduction during exposure therapy.

Findings from study 1 highlight individual variability in cognitive appraisal of events, and emphasize the importance of this appraisal in determining psychological reactions to environmental stress. Broadly, the importance of cognitive appraisal in study 1 raises the question as to whether the influence of the behavioral manipulations examined in studies 2 and 3 may be influenced by individual differences in threat perception. For example, based on their hypothesized mechanisms, the impact of the removing safety behaviors and deepening extinction should both depend on the ability of the specific stimuli selected for the manipulation to increase the perception of threat. Increasing (false) threat perception during exposure therapy should increase prediction error and boost learning. Recent research even suggests that the impact of PE-FMR may also be dependent on the level of prediction error (difference between perceived threat and actual events) invoked during the retrieval trial (Sevenster, Beckers, & Kindt, 2013). It will then be important for exposure therapy augmentation research related to each of these three behavioral manipulations (deepened extinction, PE-FMR, and safety behaviors) to account for individual differences in the perceptions of these behavioral manipulations. Although it might increase variability in procedures, we may be able to

strengthen the findings of behavioral augmentation research in exposure therapy by tailoring the procedure based on an individualized functional analysis of behavioral manipulations. This will help ensure that we maximize threat perception (and thus prediction error) for the individual patient, and thereby optimize the behavioral manipulations to improve exposure therapy outcomes. Indeed, the strongest treatment augmentation effect from the program of research in this dissertation (i.e., the beneficial effect of fading participant-identified, idiosyncratic safety behaviors) was driven by a series of studies that tailored the behavioral manipulation to the individual. Although this increased tailoring of behavioral manipulations runs the risk of increasing variability due to differences in procedures, it will come with the benefit of increasing the potency of experimental manipulations. This individualized functional analysis and tailoring of behavioral manipulations has the potential to produce more potent methods of enhancing exposure therapy in future studies.

Conclusions and Future Directions

Findings from the studies in this dissertation suggest several key areas for future research. Results from study 1 suggest the possibility of using threat perception as a marker of populations at increased risk for the development of PTSD symptoms, particularly among individuals exposed to high levels of environmental stress. Correcting overgeneralized threat perception, possibly through cost-efficient, computer-based strategies (e.g., Lester, Field, & Muris, 2011; Muris, Huijding, Mayer, & Remmerswaal, 2009) is one potential target area for future work in the prevention of anxiety disorders. Furthermore, meta-analytic findings from study 2 provide strong evidence in favor of removing safety behaviors over the course of exposure therapy, and given their deleterious effects under certain circumstances (e.g., in phobia treatment), provide data to suggest that clinicians should be cautious when introducing safety behaviors during treatment. More research is needed to determine the relative benefits and drawbacks regarding the use of judicious safety behaviors, given that a systematic review of the literature reveals very few experimental studies in this area. Findings from study 3 did not demonstrate greater reductions in pathological fear as a result of adding PE-FMR or deepened extinction to exposure therapy, either alone or in combination. However, results suggest that PE-FMR increases the speed of fear reduction during treatment. If findings extend from single session to multi-session exposure therapy protocols, PE-FMR may be a useful strategy for facilitating the speed of fear reduction. Increasing the speed of fear reduction could reduce dropout prior to treatment response by (a) reducing the number of sessions needed for treatment response, and (b) increasing treatment buy-in by facilitating successful experiences earlier in the course of therapy. Findings from each of the studies in this program of research highlight critical areas for future work, to continue to push the

envelope on the development of strategies to prevent and treat pathological fear across anxiety-related disorders.

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